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ORIGINAL CONTRIBUTION

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Characterisation with stable isotopes of the presence of a lag phase in the gastric emptying of liquids

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Summary *Background* Gastric emptying of non-nutrient liquids usually lacks the presence of an initial delay phase (lag phase), and so it has been considered to be monoexponential with an initial rapid phase followed by a slower emptying phase. However a lag phase in the gastric emptying of liquids can be found if there is a high caloric density in the liquid meal. *Aim of the study* To characterise with stable isotopes the presence of a lag phase in the gastric emptying of non-solid meals. *Methods* Healthy volunteers ingested a low caloric liquid meal (345 KJ/200 mL) (LCLM), a high caloric liquid meal (1135 KJ/180 mL) (HCLM) or a semisolid meal (1403 KJ/500 mL) (SSM). Test meals were labelled with ^{13}C-acetate. Breath samples were collected for $^{13}CO_2$ measurement and data were fitted to a power exponential function. *Results* Non-solid meals can have different behaviour related to the initial emptying. The presence of a lag phase in the gastric emptying of liquids was not masked by the processing of the tracer previous to its detection in breath. While the LCLM and SSM showed a rapid initial emptying phase (no lag phase), the HCLM has an initial slow emptying phase. The slower gastric emptying of the HCLM compared to the SSM was related to the presence of a lag phase in the gastric emptying of the HCLM. *Conclusions* The ^{13}C-acetate breath test is very accurate to identify and study the lag phase if present of liquid meals.

Key words Gastric emptying – Liquid meal – Lag phase – Stable isotopes

Introduction

Gastric emptying is a complex process with different mechanisms of emptying for liquids and solids [1, 2]. The emptying of solids is mainly dependent on the antral pressure activity, while the emptying of liquids is regulated by tonic contractions of the fundus. In addition, other factors regulate the delivery of liquids into the small bowel [1–3]. The delivery of solids from the stomach into the duodenum has been shown to be biphasic, with an initial delay (lag phase) followed by a linear emptying phase [4–6]. This lag phase is influenced by the food particle size, the caloric content of the meal, drugs and diseases [4].

Gastric emptying of liquids usually lacks the presence of this delay phase, and so it has been considered to be monoexponential with an initial rapid phase followed by a slower emptying phase [1, 6]. The presence of a lag phase in the gastric emptying of liquids and semisolids is not frequently found. When it is found, it is generally associated with the presence of fat in the liquid meal [3]. The emptying of dietary fats follows a similar pattern as solids [3]. Drugs like sumatriptan [8, 9] can also modify the lag phase of liquids.

In the recent years, stable isotopes have been used to study gastric emptying of solids (^{13}C-octanoate) [10–13], semisolids and liquids (^{13}C-acetate, ^{13}C-glycine) alone or in a mixed meal [7, 14, 15]. These stable isotopes breath tests have been compared with other methods like radioscintigraphy [7, 11, 14, 15]. The pattern of gastric emptying of solids has been studied, and the lag time and half emptying time have been described with breath tests [11]. In addition, the half emptying time of liquids and semisolids has been determined [15, 16], but the presence of a lag phase have not been completely characterised. The aim of the present work was to characterise with stable isotopes the presence of a lag phase in the gastric emptying of non-solid meals. For this purpose, we used the ^{13}C-acetate to study the pattern of gastric emptying of liquids and semisolids.

Material and methods

Test meal

All healthy volunteers performed the test after an overnight fast. Groups of volunteers had similar related anthropomorphic parameters. Nine volunteers ingested a low caloric liquid meal (LCLM): orange juice. Nine volunteers ingested a high caloric liquid meal (HCLM): Ensure Plus HN (Abbott, Holland). Nineteen volunteers ingested a yogurt meal that was considered as a semisolid meal (SSM). The composition of the meals is shown in Table 1. Liquid meals were doped with 100 mg of ^{13}C-acetate and the semisolid meals were doped with 150 mg of ^{13}C-acetate (Cambridge Isotope Laboratories, Woburn, MA).

Measuring techniques and mathematical analysis

Breath samples were collected for $^{13}CO_2$ measurement before the intake of the meal, every 5 minutes during the first hour and every 15 minutes after the first hour. The $^{13}CO_2$ breath enrichment was determined by isotope ratio mass spectrometry (Breathmat Plus, Finnigan, Germany). CO_2 production was assumed to be 300 mmol per square meter per hour and the body surface area was calculated according to the formula of Haycock et al. [17]. Data were expressed as percentage of $^{13}CO_2$ excretion in breath per hour and as percentage of $^{13}CO_2$ cumulative excretion.

Table 1 Characteristics of the test meals used

	Low caloric liquid meal (LCLM)	High caloric liquid meal (HCLM)	Semisolid meal (SSM)
Meal	Orange juice	Ensure plus NH	Yogurt
Energy	345 KJ	1135 KJ	1403 KJ
Proteins	1.2 g	11.25 g	18.8 g
Fats	–	9 g	15.28 g
Carbohydrates	20 g	36 g	30.2 g
Volume	200 mL	180 mL	500 mL

The percentage of $^{13}CO_2$ cumulative excretion in the breath was fitted to the formula:

$$\text{Percentage } ^{13}CO_2 \text{ cumulative excretion} = m(1-e^{-kt})^{ß}$$

The percentage of $^{13}CO_2$ excretion per hour was fitted to the formula:

$$\text{Percentage } ^{13}CO_2 \text{ excretion/h} = mkße^{-kt}(1-e^{-kt})^{ß-1}$$

where t is time and m, k and $ß$ are constants [11]. The value of m represents the total cumulative $^{13}CO_2$ recovery when the time is infinite. Non-linear regression analysis of these formulas was performed using the Solver program (Excel 5.0 program, Microsoft Corp., Redmond, WA).

The lag phase was determined by the formula: $t_{lag} = (\ln ß)/k$ [4, 11]. Gastric half-emptying time of the breath test was determined by the formula: $t_{1/2} = (-1/k)\ln(1-2^{-1/ß})$ [11]. The rate of emptying was the difference between the $t_{1/2}$ and the t_{lag} [8]. $t_{1/2}$ and t_{lag} were corrected ($t_{1/2corr}$ and $t_{lag\ corr}$, respectively) taking into account the 53 min required for absorption, metabolism and excretion of ^{13}C-acetate [15].

Gastric emptying parameters were expressed using the median and interquartile range. Comparisons of results were performed using non-parametric statistic (Mann-Whitney U test and sing test).

Results

The $^{13}CO_2$ excretion curves in breath after ingestion of different meals are shown in Fig. 1. A clear difference could be observed in the pattern of $^{13}CO_2$ recovery curves that represents the pattern of gastric emptying of these meals. There was an initial delay in the gastric emptying of HCLM compared with the rapid onset of the other two test meals studied. After the peak excretion of $^{13}CO_2$ the LCLM showed a rapid initial emptying followed by a period of slower emptying, but with the HCLM and the SSM there was a more linear emptying.

The values of gastric emptying parameters are shown in Table 2. The lag phase was characterised by the parameters ß and k. There was a statistical difference in the ß value between HCLM and the SSM ($p<0.05$), but not between the two types of liquid meals studied, HCLM and LCLM. However there was a statistical difference in the k values between the HCLM and the LCLM ($p<0.01$), and there was no difference between the HCLM and the SSM. There was no difference in the t_{lag} between the SSM and the LCLM ($p>0.05$), while the HCLM had a higher lag time compared with the LCLM and the SSM ($p<0.01$).

Three volunteers ingested 200 mL of water doped with ^{13}C-acetate. The calculated half time for absorption and oxidation of ^{13}C-acetate (57 min) was similar to that obtained by Braden after the intraduodenal administration of this solution [15]. After subtracting the time for absorption and metabolism for ^{13}C-acetate to $^{13}CO_2$ the lag phase for

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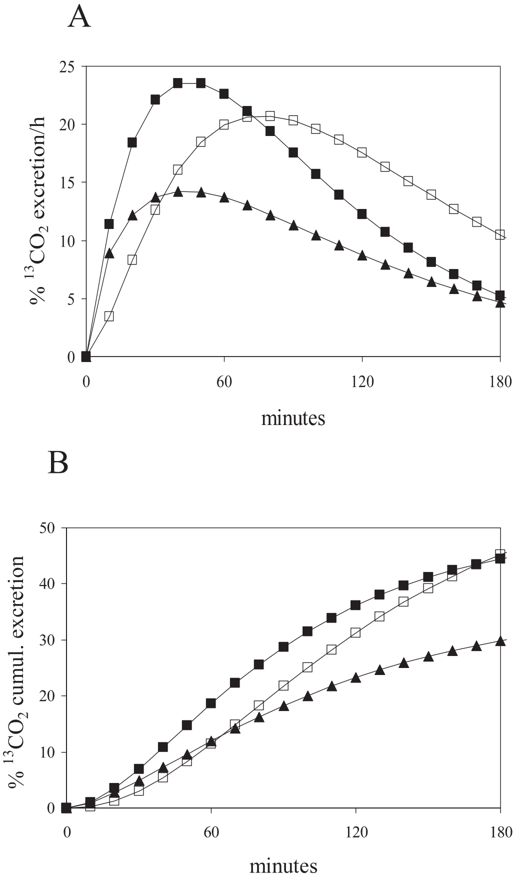

Fig. 1 Median values of $^{13}CO_2$ excretion curves after ingestion of different non-solid meals doped with ^{13}C-acetate. **A** Percentage of $^{13}CO_2$ excretion per hour. **B** Percentage of $^{13}CO_2$ cumulative excretion (■: Low caloric liquid meal; □: High caloric liquid meal; ▲: Semisolid meal).

LCLM and SSM was absent (Table 2). However, there were five out of the nineteen individuals with a positive $t_{lag\ corr}$ for the SSM.

The rate of emptying ($t_{1/2}$–t_{lag}) represents a measurement of the gastric emptying without considering the initial lag phase. There was no statistic difference between the rate of emptying and the $t_{1/2\ corr}$ in either of these two groups without a positive lag phase, that is LCLM and SSM. The HCLM showed a positive $t_{lag\ corr}$, and within this group the $t_{1/2\ corr}$ was statically higher ($p<0.05$) than the rate of emptying. Only one volunteer who ingested the HCLM lacked this lag phase, and the rate of emptying (37 min) was similar to the $t_{1/2\ corr}$ (35 min).

The SSM had a faster emptying of the remaining meal than the HCLM ($p<0.05$), although this meal had less caloric content (Table 2). To know if the difference in the gastric emptying was due to the presence of a lag phase, we compared the rate of emptying of each meal. There was no statistic difference in the rate of emptying between the HCLM and the SSM ($p>0.05$). The value of the $t_{lag\ corr}$ of the HCLM was similar to the difference between the $t_{1/2}$ of the HCLM and the SSM (27 min).

Discussion

The scintigraphy decay curve of gastric emptying is similar, but inverse, to the cumulative $^{13}CO_2$ excretion curve obtained with the breath test [4, 11, 15, 18]. The power exponential function expresses the shape characteristics of the gastric emptying curve [4, 11, 19, 20]. In the breath tests the lag phase is reflected by a late onset or a slow increase in the $^{13}CO_2$ excretion curve before the rapid exhalation of the label in breath [11, 15]. This phase is characterised by the time that corresponds to the inflection point of the cumulative $^{13}CO_2$ excretion curve. It also coincides with the time of the peak of the $^{13}CO_2$ excretion curve per hour [11].

In scintigraphy, the lack of a lag phase in the gastric emptying is indicated by a value of $ß<1$ [4], while with stable isotopes ß is always higher than 1 [15]. With the use of breath tests there is a delay in the emptying parameters, t_{lag} and $t_{1/2}$, compared with the data obtained by scintigraphy [11, 15]. This difference is related to the time for absorption and oxidation of the labelled molecule and it is independent of the lag phase of the gastric emptying [21]. Our results with the breath test indicate that the existence of a lag phase is determined by the parameters k and ß when the gastric emptying of liquids is measured with stable isotopes. The initial value of ß did not determine the presence of a lag phase because the $^{13}CO_2$ excretion curves

Table 2 Gastric emptying parameters of the different meals studied. All results are expressed as median (25th percentile – 75th percentile). Compared with HCLM: * $p<0.05$; ** $p<0.01$. Compared with SSM: § $p<0.01$

	Low caloric liquid meal (LCLM)	Semisolid meal (SSM)	High caloric liquid meal (HCLM)
ß	2.02 (1.84–2.46)	1.68 (1.46–2.34)*	2.57 (2.19–2.97)
K	0.95 (0.89–1.03)** §	0.72 (0.66–0.81)	0.74 (0.62–0.79)
t_{lag} (min)	45 (35–50)**	46 (33–55)**	80 (65–97)
$t_{1/2}$ (min)	78 (69–81)** §	94 (83–102)**	125 (112–134)
$t_{lag\ corr}$ (min)	–	–	27 (12–44)
$t_{1/2\ corr}$ (min)	24 (13–29)** §	41 (30–49)**	72 (59–81)
Rate of emptying	33 (25–33)** §	46 (37–54)	39 (38–48)

not only reflected the gastric emptying but also the absorption and oxidation of ^{13}C-acetate.

Ghoos *et al*. subtracted a time corresponding to the half time for absorption and oxidation of octanoic acid to calculate the corrected lag time ($t_{lag\ corr}$) [11]. Braden *et al*. calculated the half time for absorption and oxidation of ^{13}C-acetate after intraduodenal administration, which was determined to be 53 minutes [15]. Acetate is readily absorbed in the intestine and metabolised in humans [22]. We corrected the time for absorption and oxidation of the tracer using 53 min. The purpose of this was to study the presence of a real delay phase in the gastric emptying of liquids [15]. As stated by other authors there was not a lag phase in the gastric emptying of liquids when the caloric load was low [7, 9, 21, 23]. There was also no lag phase with the semisolid meal [15], but some volunteers showed an individual delay time. Yogurt in the stomach behaves different than milk, forming a uniform viscous phase in the stomach, and this characteristic can affect the emptying from the stomach [24]. We found a characteristic lag phase when the study of gastric emptying is performed with the HCLM and only in this group was the rate of emptying statistically lower than the $t_{lag\ corr}$. The differences of the meals relating the initial emptying can be seen in Fig. 1.

Some studies describe a lag phase employing a high caloric liquid meal [3, 25]. As the initial delay time is short, it can be lost if the measurements are performed at large intervals of time. Breath tests are easy to accomplish and samples can be obtained at short time intervals. The HCLM empties from the stomach slower than the SSM. This could be related to the presence of the lag phase in the gastric emptying of the HCLM, as the difference in the $t_{1/2}$ of the two meals was similar to the $t_{lag\ corr}$ of the HCLM. In addition, the rate of emptying (the $t_{1/2}$ minus t_{lag}) was not statically different between these two meals. It should be noted that the fat and total energetic content of the HCLM was lower than the SSM. The delay in the gastric emptying is not only dependent on the caloric content but other factors can also influence gastric emptying like volume and gravity [1, 4]. However, the physiological meaning of the lag phase is different to that of solids. The lag phase for solids is considered as the time necessary for processing the food to particles small enough to be handled as liquids [4, 5]. The existence of a lag phase for the HCLM could be explained by the presence of a high fat and caloric content per volume that induces a delayed emptying [3, 14, 25]. The intragastric separation of oil from the aqueous phase does not seem to be the cause of the lag phase due to the chemical characteristics of the HCLM [26–28]. The composition of these commercial meals includes compounds with emulsifying capacity.

In general, gastric emptying of solids is more sensitive than liquids in detecting emptying alterations but in some circumstances liquids emptying is more frequently abnormal than those of solids [1, 28–30]. Many studies of the emptying of liquids have not identified the lag phase, making it difficult to say if the acceleration or delay in gastric emptying is due to an alteration in the lag phase or in the slope of emptying [3, 8].

This work shows that the delay in the gastric emptying of liquids is not masked by the processing of the tracer previous to its detection in breath. The ^{13}C-acetate breath test is very accurate to identify and study the lag phase of liquid meals when it is present, and shows that different nonsolid meals have distinct behaviours related to the initial emptying.

Bibliography

1. Horowitz M, Fraser RJ (1995) Gastroparesis: diagnosis and management. Scand J Gastroenterol (Suppl) 213:7–16
2. Read NW, Houghton LA (1989) Physiology of gastric emptying and pathophysiology of gastroparesis. Gastroenterol Clin North Am 18:359–373
3. Houghton LA, Mangnall YF, Read NW(1990) Effect of incorporating fat into a liquid test meal on the relation between intragastric distribution and gastric emptying in human volunteers. Gut 31:1226–1229
4. Siegel JA, Urbain JL, Adler LP, Charkes ND, Maurer AH, Krevsky B, Knight LC, Fisher RS, Malmud LS (1988) Biphasic nature of gastric emptying. Gut 29:85–89
5. Christian PE, Datz FL, Moore JG (1991) Confirmation of short solid-food lag phase by continuous monitoring of gastric emptying. J Nucl Med 32:1349–1352
6. Collins PJ, Horowitz M, Cook DJ, Harding PE, Shearman DJ (1983) Gastric emptying in normal subjects-a reproducible technique using a single scintillation camera and computer system. Gut 24:1117–1125
7. Maes BD, Ghoos YF, Geypens BJ, Mys G, Hiele MI, Rutgeerts PJ, Vantrappen G (1994) Combined carbon-13-glycine/carbon–14-octanoic acid breath test to monitor gastric emptying rates of liquids and solids. J Nucl Med 35:824–831
8. Houghton LA, Fowler P, Keene ON, Read NW (1992) Effect of sumatriptan, a new selective 5HT1-like agonist, on liquid gastric emptying in man. Aliment Pharmacol Ther 6:685–691
9. Coulie B, Tack J, Maes B, Geypens B, De Roo M, Janssens J (1997) Sumatriptan, a selective 5-HT1 receptor agonist, induces a lag phase for gastric emptying of liquids in humans. Am J Physiol 272:G902–G908
10. Schadewaldt P, Schommartz B, Wienrich G, Brosicke H, Piolot R, Ziegler D (1997) Application of isotope-selective nondispersive infrared spectrometry (IRIS) for evaluation of [13C]octanoic acid gastric-emptying breath tests: comparison with isotope ratio-mass spectrometry (IRMS). Clin Chem 43:518–522
11. Ghoos YF, Maes BD, Geypens BJ, Mys G, Hiele MI, Rutgeerts PJ, Vantrappen G (1993) Measurement of gastric emptying rate of solids by means of a carbon-labeled octanoic acid breath test. Gastroenterology 104:1640–1647
12. Perri F, Clemente R, Festa V, Andriulli A (1998) 13C-Octanoic acid breath test: valueless test for gastric emptying. Gastroenterology 114:857–859
13. Choi MG, Camilleri M, Burton DD, Zinsmeister AR, Forstrom LA, Nair KS (1997) [13C]octanoic acid breath test for gastric emptying of solids: accuracy, reproducibility, and comparison with scintigraphy. Gastroenterology 112:1155–1162
14. Mossi S, Meyer-Wyss B, Beglinger C, Schwizer W, Fried M, Ajami A, Brignoli

R (1994) Gastric emptying of liquid meals measured noninvasively in humans with [13C]acetate breath test. Dig Dis Sci 39:107S–109S

15. Braden B, Adams S, Duan LP, Orth KH, Maul FD, Lembcke B, Hor G, Caspary WF (1995) The [13C]acetate breath test accurately reflects gastric emptying of liquids in both liquid and semisolid test meals. Gastroenterology 108:1048–1055
16. Vesa TH, Marteau PR, Briet FB, Flourie B, Briend A, Rambaud JC (1997) Effects of milk viscosity on gastric emptying and lactose intolerance in lactose maldigesters. Am J Clin Nutr 66:123–126
17. Haycock GB, Schwartz GJ, Wisotsky DH (1978) Geometric method for measuring body surface area: a height-weight formula validated in infants, children, and adults. J Pediatr 93:62–66
18. Maurer AH, Malmud LS, Fisher RS (1995) Radionuclide scintigraphy of the intestinal tract. In: Haubrich WS, Schaffner F, Berk JE (eds) Bokus Gastroenterology, 5th edn. WB Saunders Comp, Philadelphia, Vol. 1. pp 221–237
19. González A, Monreal I, Mugueta C, Gil MJ, Betés M, Varo N (1988) Estudio del vaciamiento gastrico de sólidos y líquidos mediante el empleo de isótopos estables. Rev Med Univ Navarra 42:83–90
20. Elashoff JD, Reedy TJ, Meyer JH (1982) Analysis of gastric emptying data. Gastroenterology 83:1306–1312
21. Duan LP, Braden B, Caspary WF, Lembcke B (1995) Influence of cisapride on gastric emptying of solids and liquids monitored by 13C breath tests. Dig Dis Sci 40:2200–2206
22. Katz J (1985) Determination of gluconeogenesis in vivo with 14C-labeled substrates. Am J Physiol 248:R391–R399
23. Smith JL, Jiang CL, Hunt JN (1984) Intrinsic emptying pattern of the human stomach. Am J Physiol 246:R959–R962
24. Mahé S, Marteau P, Huneau JF, Thuillier F, Tomé D (1994) Intestinal nitrogen and electrolyte movements following fermented milk ingestion in man. Br J Nutr 71:169–180
25. van Berge-Henegouwen MI, van Gulik TM, Akkermans LM, Jansen JB, Gouma DJ (1997) The effect of octreotide on gastric emptying at a dosage used to prevent complications after pancreatic surgery: a randomised, placebo controlled study in volunteers. Gut 41:758–762
26. Jian R, Ducrot F, Piedeloup C, Mary JY, Najean Y, Bernier JJ (1985) Measurement of gastric emptying in dyspeptic patients: effect of a new gastrokinetic agent (cisapride). Gut 26:352–358
27. Edelbroek M, Horowitz M, Maddox A, Bellen J (1992) Gastric emptying and intragastric distribution of oil in the presence of a liquid or a solid meal. J Nucl Med 33:1283–1290
28. Maes BD, Hiele MI, Geypens BJ, Ghoos YF, Rutgeerts PJ (1998) Gastric emptying of the liquid, solid and oil phase of a meal in normal volunteers and patients with Billroth II gastrojejunostomy. Eur J Clin Invest. 28:197–204
29. Vantrappen G (1994) Methods to study gastric emptying. Dig Dis Sci 39:91S–94S
30. Smout A, Horowitz M, Armstrong D (1994) Methods to study gastric emptying. Frontiers in gastric emptying. Dig Dis Sci 39:S130–132