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Breath tests for the assessment of the orocecal transit time

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Abstract. **Orocecal transit time (OCTT) is one of the main determinant of the hunger ratings and gastrointestinal sensitivity. While marked-isotopes scintigraphy is the gold standard in its determination in the clinical frame, breath tests are cheap, well-tolerated and non-invasive alternatives. In fact C-13 and C-14 stable isotopes breath tests can be used to assess gastric emptying and OCTT in the clinical and research frames. Moreover, hydrogen (H2) lactulose breath test can be used to assess OCTT in the research frame only due to its laxative action; inulin breath test, devoid of this bias, could be replacing it. However, the main limitation in the use of breath tests in the OCTT determination is their low reproducibility.**

Keywords:

Lactose ureyde, Octanoate, Lactulose, Inulin, OCTT.

Introduction

Marked isotopes scintigraphy is the gold standard for the assessment of gastric emptying and total OCTT. It is a pretty cheap investigation but quite time consuming and not devoid of limitations for the patient such as its use in pregnant women and children[1]. In order to overcome these limitations they have been ruled out several stable-isotopes and hydrogen (H2) breath tests[2,3] for the determination of gastric emptying, one of the main component of the upper GI tract motility involved in the control of hunger and nutrient acquisition in man[4], and for the total orocecal transit time (OCTT), involved in the regulation of gastrointestinal sensitivity and motility together with the migrating motor complex (MMC)[5].

This review describes technical and experimental/clinical applications of C-13, C-14 and H2 breath tests for the assessment of gastric emptying and OCTT in man.

C-14 octanoate and C-13 glycine breath tests

General principles

14C-octanoic acid breath test (14C-OBT) is able to measure gastric emptying of solids based on[6] the retention of 14C-octanoic acid in the solid phase of a standard test meal (egg yolk) during its passage in the stomach, followed by[7] a rapid disruption in the duodenum with[8] subsequent absorption of 14C-octanoic acid in the mesenteric vessels and consequent[9] hepatic oxidation to $14CO_2$[3]. Thus, the appearance of $14CO_2$ in breath after oral administration of 14C-octanoic depends on the gastric emptying of the egg yolk into the duodenum[10].

A percentage of dose/h curve after ingestion of a 14C-octanoic acid labeled solid test meal is characterized by an ascending slope, a peak of excretion, and a descending exponential slope[3].

Ghoos et al[10] validated the 14C-OBT against scintigraphy, the gold standard technique to evaluate gastric emptying of solids. Both volunteers and dyspeptic subjects were given standard test meal consisting of a scrambled egg whose yolk was doped with 14C-octanoic acid and the egg white labeled with ^{99m}Tc albumin colloid.

Interestingly, both within-subject variability (inter-individual variability) and between-subject variability (day to day variability) were small and not statistically significant.

13C-glycine breath test can be used as marker of the liquid phase of gastric emptying because it is easily solubilized in water[3,11] and rapidly absorbed and converted into $13CO_2$ after it enters the small bowel. Moreover, the use of glycine breath test allows simultaneous measurement of both the solid and liquid phase of the meal, in association with 14C-octanoic acid.

Glycine is not absorbed in the stomach; the site of absorption of glycine and other neutral amino acids is located in the proximal intestine, using mainly active transport mechanisms[3,12]. After

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transport across the intestinal wall, glycine is partly oxidized to CO_2 by different pathways[3,13,14].

The dose/h curve after ingestion of a 13C-glycine labeled liquid test meal is similarly characterized by an ascending slope, a peak of excretion, and a descending exponential slope[3].

The 13C-glycine breath test compares favorably with other tests of liquid gastric emptying, e.g. aspiration technique[15], radioscintigraphy[1-3], paracetamol absorption test[16], the echographic method[17] and the recent MRI technique[3,18].

The good correlation of both the breath-test-determined gastric half-emptying time and the peak excretion time with the radioscintigraphic half-emptying time depends on the fact that these two breath-test parameters are independent of the endogenous CO2 production and on the amount of 13C-glycine converted to CO_2[1-3].

Clinical applications

The 14C-OBT and 13C-glycine breath test are useful tools to evaluate gastric emptying either in physiological and in pathological states; they are also able to detect changes in gastric emptying induced by drugs such as motilin-receptor agonists, cisapride, anticholinergics, and octreotide[3,10-13]. In addition OBT has been also used to evaluate differences in the physiology of gastric emptying of solids and liquids in both adults and children. The OBT has been also employed to study the effects of gastric emptying on the rate of intraluminal lipolysis (tested with 13C-"mixed trigliceride"-breath test) in patients with pancreatic insufficiency[18] and the rate of ureolysis (tested with 13Curea breath test) in *Helicobacter pylori* infected and uninfected subjects[1-3,18].

For example in patients with distal gastrectomy, an early dumping of the oil phase of the meal was observed compared to healthy controls[19].

In patients with non-ulcer dyspepsia[20] about 30% of them had a delayed gastric emptying as compared to controls. In another group of dyspeptic patients studied by the OBT[21] almost one third of them displayed a significant delay in gastric emptying, significantly correlated with symptoms such as postprandial fullness, nausea, and vomiting. Children with celiac disease, studied by the OBT before and after gluten-free diet[22] presented a significantly delayed gastric emptying as compared with healthy age-matched controls. After 6 months of gluten-free diet, gastric emptying parameters returned to normal range in patients.

As cited above similar clinical applications can be performed with 13C-glycine breath test. In fact, although there is lacking information about intragastric distribution of the different phases of the test meal, breath-test measurements of gastric emptying offer several advantages over radioscintigraphic techniques.

C-13 lactose ureyde breath test

General principles

Radioscintigraphy is usually considered the reference technique for measuring OCTT. However, as mentioned above, several draw backs limit its application in routine clinical practice: relevant costs, time and specialized personnel are required, and, least but not last, the use of radioactive isotopes is associated with some irradiation risk (<3 mSv). Therefore, it is conceivable to avoid repeating the exam at short intervals especially in children while pregnant women that should avoid it at all[1].

Breath tests involving the stable carbon isotope, 13C have been successfully introduced with several clinical and research applications, including gastric emptying, as described above[10]. Glycosyl ureides have been studied extensively for their physical and chemical properties[1,23]. In fact, the enzymes of the brush border of the human intestine are not able to split the bond of sugars to urea. Because glycosyl ureides are only slightly absorbed in the small bowel without further metabolism, they can reach the large bowel unaltered. On the other hand, colonic flora is able to split the bond of sugars to urea[24,25] and, subsequently produce, among the other products, CO_2, free in the breath of the host as $13CO_2$. Therefore, breath sampling after oral administration of the labeled molecule, at regular time intervals for approximately ten hours, allows the time of appearance of the label in breath to be defined. This point in time indicates the time needed by the marker molecule, together with the meal in which it was integrated, to reach the cecum[26].

In the validation paper by Geypens et al[1] OCTT results from scintigraphy (mean OCTT= 283±53 min) and breath test (mean OCTT= 292±58 min) correlated well (r = 0.94). Altman-Bland statistics showed close agreement between scintigraphy and breath test. No significant difference between male and female subjects was observed.

Open issues in the application of this breath test are represented by a diminished response after use of antibiotics and an altered response after laxatives[27]. In patients with bacterial overgrowth, the substrate may be split in the small intestine and yield a falsely accelerated transit time. Wutzke et al[28] have compared the LUBT and the lactulose H2 breath test in healthy adults. They demonstrated that the lactulose H2 breath test resulted in a statistically significant shorter OCTT (1.18 hours) in comparison with the LUBT. Finally, LUBT remains the only validated breath test for clinical and research examination in man although one limitation is its duration (approximately 10 hours) and substrates costs.

Clinical applications

To date, there are a few clinical trials using this breath test. However, the test is suitable for studying the influences of pharmaceuticals and nutrients on intestinal motility both in adults and children. In particular, children studies have highlighted technical issues of LUBT with different results according to the experimental setup. The validation study by Geypens et al[1] and the subsequent study in dyspeptic children[27] have showed that those used setup clearly allow a good clinical reproducibility and avoid the laxative effect of lactulose breath test in comparison with scintigraphy.

H2 breath tests for the assessment of OCTT

General principles

The appearance in the expiratory breath of hydrogen (H2) produced by colonic fermentation of an ingested liquid or solid sugar compound may be used to measure OCTT[29-34].

In fact, a solution containing 10 g of lactulose in 100 mL of water or a solid meal containing baked beans as a source of non-absorbable carbohydrate (stachyose and raffinose) is most often used[29,35,36] The outcome of reproducibility test with the liquid meal is poorer than with the solid meal[29,37,38]. The major factor determining the poor reproducibility of the liquid meal is the phase of the interdigestive migrating motor complex[39]. Transit time with the solid meal is significantly longer than with the liquid meal because the addition of lactulose to a solid meal accelerates small bowel transit[40].

Ingestion of the test-meal is followed by a biphasic breath hydrogen profile: the first peak follows the meal; the second, associated with the meal entering the caecum, normally occurs hours later. Increments of 3, 5 or 10 ppm of hydrogen above baseline maintained or increased in the two following determinations are considered the incoming of the meal in the caecum[29,41].

The OCTT in healthy subjects ranges respectively between 40 and 170 min for the liquid[29] and between 192 and 232 min for a solid meal[29,35,36]. The 10 g lactulose dosage for the liquid test has been chosen due to its prokinetic effects eliciting at increasing doses[29]. The current protocol employing the liquid solution includes 10 g of lactulose in 100 mL of water, and a cut-off value of hydrogen ≥10 ppm (based on barium meal studies) followed by at least two other subsequent increments[42].

About 5-27% of normal subjects fail to produce an increment of hydrogen breath concentration after the meal due to the absence of hydrogen-producing colonic microflora and, probably, due to the presence of a metanogenic-one[2,29,43]. The menstrual cycle may influence the OCTT[29,44].

Inulin, a natural polysaccharide with a higher degree of polymerisation than lactulose and, consequently, less active osmotically, has been proposed as an ideal substrate to be added to a solid meal for OCTT assessment[29,45,46]. Thus, in contrast with lactulose, inulin does not shorten OCTT (ranging between 420 and 570 min after ingestion of 5 or 10 g inulin with the solid meal).

H2 breath tests are generally safe but bloating and abdominal distension may occur after colonic fermentation of lactulose[47].

Potential applications to the clinical and experimental setting

Although non-invasive, safe, cheap and easy to perform, the main limitation for the clinical application of the hydrogen-breath test to estimate OCTT is due to the wide results variability in healthy volunteers over the rather low liquid test reproducibility[2,29].

A delayed oro-caecal transit assessed by hydrogen breath test has been reported in various subgroups of patients, including those with depression[29], chronic alcoholism[48], constipation[49], acromegalics[50], diabetics[51], irritable bowel syndrome[52], beta thalassemia major[53], pregnancy[50], cholecystectomy[54], obesity[55], cirrhotics[56], scleroderma, dyspeptic patients[57], and in constipated children[58,59].

By contrast, fast oro-caecal transit has been reported in patients with the irritable bowel syndrome[60], chronic alcoholics[61], partial gastrectomy[62], post-vagotomy diarrhea[63] and hyperthyroidism[64,65]. Despite such wide applications to the research field, so far recent guidelines do not suggest a definite clinical indication for the test in the clinical setting[66].

Interestingly, the test reproducibility and variability improve in the experimental setting, in particular in clinical pharmacology studies on OCTT. Transit is accelerated by misoprostol[67], erythromycin[68], metoclopramide[69] and paroxetine[29,70], and it was delayed by loperamide[71], ritodrine[72], codeine[29], dopamine[73], peppermint oil, n-butylscopolamine[74] and imipramine[75].

General conclusions and future perspectives

Breath tests for the assessment of OCTT are safe, cheap, well-tolerated and non-invasive tools.

C-13 glycine and C-14 octanoate breath tests are normally used to assess gastric liquid and solid emptying such as C-13 lactose-ureide to assess OCTT in the clinical and research frames.

H2 lactulose is normally used to assess OCTT in the research frame only, due to its laxative properties, able to shorten OCTT. Therefore, inulin breath test, if larger placebo-controlled studies will confirm the first promising validation findings, can be considered a new tool potentially replacing LBT in the H2 assessment of OCTT.

However, the main limitation in the use of breath tests in the OCTT determination is the wide values variation among normal subjects and the poor reproducibility.

Competing of interest

No competing interests for any of the authors.

References

1) Geypens B, Bennink R, Peeters M, Evenepoel P, Mortelmans L, Maes B, Ghoos Y, Rutgeerts P. Validation of the lactose-[13C]ureide breath test for determination of orocecal transit time by scintigraphy. J Nucl Med 1999; 40: 1451-1455.
2) Romagnuolo J, Schiller D, Bailey RJ. Using breath tests wisely in a gastroenterology practice: an evidence-based review of indications and pitfalls in interpretation. Am J Gastroenterol 2002; 97: 1113-1126.
3) Perri F, Pastore MR, Annese V. 13C-octanoic acid breath test for measuring gastric emptying of solids. Eur Rev Med Pharmacol Sci 2005; 9: 3-8.
4) Janssen P, Vanden Berghe P, Verschueren S, Lehmann A, Depoortere I, Tack J. Review article: the role of gastric motility in the control of food intake. Aliment Pharmacol Ther 2011; 33: 880-894
5) Deloose E, Janssen P, Depoortere I, Tack J. The migrating motor complex: control mechanisms and its role in health and disease. Nat Rev Gastroenterol Hepatol 2012; 9: 271-285.
6) Griffith GH, Owen GM, Kirman S, Shields R. Measurement of rate of gastric emptying using chromium-51. Lancet 1966; i: 1244-1245.
7) Siegel J, Wu R, Knight L, Zelac RE, Stern HS, Malmud LS. Radiation dose estimates for oral agents used in upper gastrointestinal disease. J Nucl Med 1983; 24: 835-837.
8) Bolondi L, Bortolotti M, Santi V, Colletti T, Gaiani S, Labo G. Measurement of gastric emptying by real-time ultrasonography. Gastroenterology 1985; 89: 752-759.
9) Mc-Clelland GR, Sutton JA. Epigastric impedance: a non-invasive method for the assessment of gastric emptying and motility. Gut 1985; 26: 607-614.
10) Ghoos YF, Maes BD, Geypens BJ, Mys G, Hiele MI, Rutgeerts PJ, Vantrappen G. Measurement of gastric emptying rate of solids by means of a carbon-labeled octanoic acid breath test. Gastroenterology 1993; 104: 1640-1647.
11) Maes B, Hiele M, Geypens B, Rutgeers P, Ghoos Y, Vantrappen G. Pharmacological modulation of gastric emptying rate of solids as measured by the carbon labelled octanoic acid breath tes: influence of erythromycin and propantheline. Gut 1994; 35: 333-337.
12) Duan L, Braden B, Caspary W, Lembke B. Influence of cisapride on gastric emptying of solids and liquids monitored by 13C breath tests. Dig Dis Sci 1995; 40: 2200-2206.
13) Maes B, Ghoos Y, Geypens B, Hiele M, Rutgeerts P. Influence of octreotide on the gastric emptying of solids and liquids in normal healthy subjects. Aliment Pharmacol Ther 1995; 9: 11-18.
14) Maes B, Ghoos Y, Geypens B, Hiele M, Rutgeerts P. Relation between gastric emptying rate and energy intake in children compared with adults. Gut 1995; 36: 183-188.
15) Maes B, Ghoos Y, Spitz B, Rutgeerts P, Van Assche A, Vantrappen G. Gastric emptying rate of solids in non-dyspeptic pregnant women, using the 13C-octanoic acid breath test. Gastroenterology 1993; 104: A546.
16) Veereman-Wauters G, Ghoos Y, van der Schoor S, Maes B, Hebbalkar N, Devlieger H, Eggermont E. The 13C-octanoic acid breath test: a non invasive technique to assess gastric emptying in preterm infants. J Pediatr Gastroenterol Nutr 1996; 23: 111-117.
17) Maes B, Ghoos Y, Geypens B, Hiele M, Rutgeerts P. Relation between gastric emptying rate and rate of intraluminal lipolysis. Gut 1996; 38: 23-27.
18) Perri F, Ghoos YF, Maes BD, Geypens BJ, Ectors N, Geboes K, Hiele MI, Rutgeerts PJ. Gastric emptying rate and Helicobacter pylori infection in duodenal ulcer disease. Dig Dis Sci 1996; 41: 462-468.
19) Maes B, Hiele M, Ghoos Y, Rutgeerts P. Gastric emptying in distal gastrectomy is characterized

by an early dumping of the oil phase compared to normal healthy volunteers. Gastroenterology 1994; 106: A535.

20) Maes B, Ghoos Y, Hiele M, Rutgeerts P. Gastric emptying rate of solids in patients with non ulcer dyspepsia. Dig Dis Sci 1997; 42: 1158-1162.

21) Perri F, Clemente R, Festa V, Annese V, Quitadamo M, Rutgeerts P, Andriulli A. Patterns of symptoms in functional dyspepsia: role of Helicobacter pylori infection and delayed gastric emptying. Am J Gastroenterol 1998; 93: 2082-2088.

22) Perri F, Pastore M, Zicolella A, Annese V, Quitadamo M, Andriulli A. Gastric emptying of solids is delayed in celiac disease and normalizes after gluten withdrawal. Acta Paediatr 2000; 89: 921-925.

23) Hofmann E. About the breakdown of glucose ureide by bacteria. Biochem Zeitschr 1931; 243: 416-422.

24) Goodman I. Glycosylureides. Adv Carbohydr Chem Biochem 1958; 13: 215-236.

25) Benn MH, Jones AS. Glycosyulreas Part 1.Preparation and some reactions of D-glycosylureas and D-ribosylureas. J Chem Soc 1960; 4: 3837-3841.

26) Heine WE, Berthold HK, Klein PD. A novel stable isotope breath test: a 13C-labeled glycosyl ureides used as noninvasive markers of intestinal transit time. Am J Gastronterol 1995; 90: 93-98.

27) Van Den Driessche M, Van Malderen N, Geypens B, Ghoos Y, Veereman-Wauters G. Lactose-[13C]ureide breath test: a new, noninvasive technique to determine orocecal transit time in children. J Pediatr Gastroenterol Nutr 2000; 31: 433-438.

28) Wutzke KD, Heine WE, Plath C, Leitzmann P, Radke M, Mohr C, Richter I, Gülzow HU, Hobusch D. Evaluation of orocecal transit time: a comparison of the lactose (13C, 15N) ureide 13CO2 and the lactulose H2 breath test in humans. Eur J Clin Nutr 1997; 51: 11-19.

29) Gasbarrini A, Corazza GR, Gasbarrini G, Montalto M, Di Stefano M, Basilisco G, Parodi A, Usai-Satta P, Vernia P, Anania C, Astegiano M, Barbara G, Benini L, Bonazzi P, Capurso G, Certo M, Colecchia A, Cuoco L, Di Sario A, Festi D, Lauritano C, Miceli E, Nardone G, Perri F, Portincasa P, Risicato R, Sorge M, Tursi A; 1st Rome H2-Breath Testing Consensus Conference Working Group. Methodology and indications of H2-breath testing in gastrointestinal diseases: the Rome Consensus Conference. Aliment Pharmacol Ther 2009; 29: 1-49.

30) Bond JH, Levitt MD, Prentiss R. Investigation of small bowel transit time in man utilizing pulmonary hydrogen measurements. J Lab Clin Med 1975; 85: 546-556.

31) Di Stefano M, Missanelli A, Miceli E, Strocchi A, Corazza GR. Hydrogen breath test in the diagnosis of lactose malabsorption: accuracy of new vs. conventional criteria. J Lab Clin Med 2004; 144: 313-318.

32) Rosenthal A, Solomons NW. Time-course of cigarette smoke contamination of clinical hydrogen breath-analysis tests. Clin Chem 1983; 29: 1980-1981.

33) Payne DL, Welsh JD, Claypool PL. Breath hydrogen (H2) response to carbohydrate malabsorption after exercise. J Lab Clin Med 1983; 102: 147-150.

34) Thompson DG, O'Brien JD, Hardie JM. Influence of the oropharyngeal microflora on the measurement of exhaled breath hydrogen. Gastroenterology 1986; 91: 853-860.

35) Camboni G, Basilisco G, Bozzani A, Bianchi PA. Repeatability of lactulose hydrogen breath test in subjects with normal or prolonged orocecal transit. Dig Dis Sci 1988; 33: 1525-1527.

36) Read NW, Miles CA, Fisher D, Holgate AM, Kime ND, Mitchell MA, Reeve AM, Roche TB, Walker M. Transit of a meal through the stomach, small intestine, and colon in normal subjects and its role in the pathogenesis of diarrhea. Gastroenterology 1980; 79: 1276-1282.

37) La Brooy SJ, Male PJ, Beavis AK, Misiewicz JJ. Assessment of the reproducibility of the lactulose H2 breath test as a measure of mouth to caecum transit time. Gut 1983; 24: 893-896.

38) Caride VJ, Prokop EK, Troncale FJ, Buddoura W, Wienchenbach K, McCallum RW. Scintigraphic determination of small intestinal transit time: comparison with the hydrogen breath technique. Gastroenterology 1984; 86: 714-720.

39) Di Lorenzo C, Dooley CP, Valenzuela JE. Role of fasting gastrointestinal motility in the variability of gastrointestinal transit time assessed by hydrogen breath test. Gut 1991; 32: 1127-1130.

40) Miller MA, Parkman HP, Urbain JL, Brown KL, Donahue DJ, Knight LC, Maurer AH, Fisher RS. Comparison of scintigraphy and lactulose breath hydrogen test for assessment of orocecal transit: lactulose accelerates small bowel transit. Dig Dis Sci 1997; 42: 10-18.

41) Hirakawa M, Iida M, Kohrogi N, Fujishima M. Hydrogen breath test assessment of orocecal transit time: comparison with barium meal study. Am J Gastroenterol 1988; 83: 1361-1363.

42) Lin HC, Prather C, Fisher RS, Meyer JH, Summers RW, Pimentel M, McCallum RW, Akkermans LM, Loening-Baucke V; AMS Task Force Committee on Gastrointestinal Transit. Dig Dis Sci 2005; 50: 989-1004.

43) Vogelsang H, Ferenci P, Frotz S, Meryn S, Gangl A. Acidic colonic microclimate–possible reason for false negative hydrogen breath tests. Gut 1988; 29: 21-26.

44) Wald A, Van Thiel DH, Hoechstetter L, Gavaler JS, Egler KM, Verm R, Scott L, Lester R. Gastrointestinal transit: the effect of the menstrual cycle. Gastroenterology 1981; 80: 1497-1500.

45) Geboes KP, Luypaerts A, Rutgeerts P, Verbeke K. Inulin is an ideal substrate for a hydrogen breath test to measure the orocaecal transit time. Aliment Pharmacol Ther 2003; 18: 721-729.

46) Schneider AR, Jepp K, Murczynski L, Biniek U, Stein J. The inulin hydrogen breath test accurately reflects orocaecal transit time. Eur J Clin Invest 2007; 37: 802-807.

47) Basilisco G, Marino B, Passerini L, Ogliari C. Abdominal distension after colonic lactulose fermentation recorded by a new extensometer. Neurogastroenterol Motil 2003; 15: 427-433.

48) Addolorato G, Montalto M, Capristo E, Certo M, Fedeli G, Gentiloni N, Stefanini GF, Gasbarrini G. Influence of alcohol on gastrointestinal motility: lactulose breath hydrogen testing in orocecal transit time in chronic alcoholics, social drinkers and teetotaler subjects. Hepatogastroenterology 1997; 44: 1076-1081.

49) Altomare DF, Portincasa P, Rinaldi M, Di Ciaula A, Martinelli E, Amoruso A, Palasciano G, Memeo V. Slow-transit constipation: a solitary symptom of a systemic gastrointestinal disease. Dis Colon Rectum 1999; 42: 231-240.

50) Scarpello JH, Greaves M, Sladen GE. Small intestinal transit in diabetics. Br Med J 1976; 2: 1225-1226.

51) Lawson M, Kern F Jr, Everson GT. Gastrointestinal transit time in human pregnancy: prolongation in the second and third trimesters followed by postpartum normalization. Gastroenterology 1985; 89: 996-999.

52) Portincasa P, Moschetta A, Baldassarre G, Altomare DF, Palasciano G. Pan-enteric dysmotility, impaired quality of life and alexithymia in a large group of patients meeting the Rome II criteria for irritable bowel. World J Gastroenterology 2003; 9: 2293-2299.

53) Portincasa P, Moschetta A, Berardino M, Di-Ciaula A, Vacca M, Baldassarre G, Pietrapertosa A, Cammarota R, Tannoia N, Palasciano G. Impaired gallbladder motility and delayed orocecal transit contribute to pigment gallstone and biliary sludge formation in beta-thalassemia major adults. World J Gastroenterol 2004; 10: 2383-2390.

54) Fort JM, Azpiroz F, Casellas F, Andreu J, Malagelada JR. Bowel habit after cholecystectomy: physiological changes and clinical implications. Gastroenterology 1996; 111: 617-622.

55) Basilisco G, Camboni G, Bozzani A, Vita P, Doldi S, Bianchi PA. Orocecal transit delay in obese patients. Dig Dis Sci 1989; 34: 509-512.

56) Maheshwari A, Thuluvath PJ. Autonomic neuropathy may be associated with delayed orocaecal transit time in patients with cirrhosis. Auton Neurosci 2005; 118: 135-139.

57) Di Ciaula A, Covelli M, Berardino M, Wang DQ, Lapadula G, Palasciano G, Portincasa P. Gastrointestinal symptoms and motility disorders in patients with systemic scleroderma. BMC Gastroenterol 2008; 8: 7.

58) Vajro P, Silano G, Longo D, Staiano A, Fontanella A. Orocoecal transit time in healthy and constipated children. Acta Paediatr Scand 1988; 77: 583-586.

59) Soares AC, Lederman HM, Fagundes-Neto U, de Morais MB. Breath hydrogen test after a bean meal demonstrates delayed oro-cecal transit time in children with chronic constipation. J Pediatr Gastroenterol Nutr 2005; 41: 221-224.

60) Corbett CL, Thomas S, Read NW, Hobson N, Bergman I, Holdsworth CD. Electrochemical detector for breath hydrogen determination: measurement of small bowel transit time in normal subjects and patients with the irritable bowel syndrome. Gut 1981; 22: 836-840.

61) Keshavarzian A, Iber FL, Dangleis MD, Cornish R. Intestinal-transit and lactose intolerance in chronic alcoholics. Am J Clin Nutr 1986; 44: 70-76.

62) Bond JH, Levitt MD. Use of breath hydrogen (H2) to quantitate small bowel transit time following partial gastrectomy. J LabClin Med 1977; 90: 30-36.

63) O'Brien JD, Thompson DG, McIntyre A, Burnham WR, Walker E. Effect of codeine and loperamide on upper intestinal transit and absorption in normal subjects and patients with postvagotomy diarrhoea. Gut 1988; 29: 312-318.

64) Shafer RB, Prentiss RA, Bond JH. Gastrointestinal transit in thyroid disease. Gastroenterology 1984; 86: 852-855.

65) Tobin MV, Fisken RA, Diggory RT, Morris AI, Gilmore IT. Orocaecal transit time in health and in thyroid disease. Gut 1989; 30: 26-29.

66) Rao SS, Camilleri M, Hasler WL, Maurer AH, Parkman HP, Saad R, Scott MS, Simren M, Soffer E, Szarka L. Evaluation of gastrointestinal transit in clinical practice: position paper of the American and European Neurogastroenterology and Motility Societies. Neurogastroenterol Motil 2011; 23: 8-23.

67) Minocha A, Katragadda R, Rahal PS, Ries A. Erythromycin shortens orocaecal transit time in diabetic male subjects: a double-blind placebo-controlled study. Aliment Pharmacol Ther 1995; 9: 529-533.

68) Staniforth DH. Effect of drugs on oro-caecal transit time assessed by the lactulose/breath hydrogen method. Eur J Clin Pharmacol 1987; 33: 55-58.

69) Gorard DA, Libby GW, Farthing MJ. Influence of antidepressants on whole gut and orocaecal transit times in health and irritable bowel syndrome. Aliment Pharmacol Ther 1994; 8: 159-166.

70) Basilisco G, Bozzani A, Camboni G, Recchia M, Quatrini M, Conte D, Penagini R, Bianchi PA. Effect of loperamide and naloxone on mouth-to-caecum transit time evaluated by lactulose hydrogen breath test. Gut 1985; 26: 700-703.

71) Basilisco G, Camboni G, Bozzani A, Paravicini M, Bianchi PA. Oral naloxone antagonizes loperamide-induced delay of orocecal transit. Dig Dis Sci 1987; 32: 829-832.

72) Basilisco G, Camboni MG, Bozzani A, Molgora M, Bianchi PA. Single doses of ritodrine delay orocaecal transit in patients with irritable bowel syndrome. Br J Clin Pharmacol 1990; 29: 355-358.

73) Thompson DG, O'Brien JD, Hardie JM. Influence of the oropharyngeal microflora on the measurement of exhaled breath hydrogen. Gastroenterology 1986; 91: 853-860.

74) Levein NG, Thorn SE, Wattwil M. Dopamine delays gastric emptying and prolongs orocaecal transit time in volunteers. Eur J Anaesthesiol 1999; 16: 246-250.

75) Goerg KJ, Spilker T. Effect of peppermint oil and caraway oil on gastrointestinal motility in healthy volunteers: a pharmacodynamic study using simultaneous determination of gastric and gallbladder emptying and orocaecal transit time. Aliment Pharmacol Ther 2003; 17: 445-451.