**Online supplement:**

**Results of Comparison between drink tests**

In the majority of studies, regardless of the substrate and speed, men have higher drink test volume tolerance than women (Figure 2). Most of the studies showed a higher intake of water compared to nutrient drink (8-10, 12). In the study by Boeckxstaens et al., a significant correlation was found between the volume ingested in the rapid water drink test and the rapid nutrient drink test. In the study by Abid et al., somewhat paradoxically, drinking a nutrient drink at a slower rate induced satiety at a lower volume than when drinking at a rapid rate (10). They considered the slow nutrient drink test superior as it was not influenced by body mass index or age and was associated with the highest symptom load (10).

**Results of Relation with pathophysiological mechanisms**

Boecxkstaens *et al.* studied the correlation of the rapid water drink test with gastric barostat studies in FD and HV. The authors found a significant correlation between sensitivity to gastric distention and the maximum tolerated water volume (R=0.48, p<0.0001) (8). Similarly, for the rapid nutrient drink test, a significant correlation was found between sensitivity to gastric distention measured with the barostat and the maximum tolerated nutrient volume (R=0.36, p=0.001) (8). However, the sensitivity and specificity of the rapid drink tests to predict visceral hypersensitivity were low. The rapid nutrient or water drink test volume was not correlated to GA as measured with the barostat (8).

Tack *et al*. studied the correlation of the satiety drinking test with gastric barostat findings in HV and FD patients (15). The endpoint of the satiety drinking test (i.e. using delivery from a peristaltic pump) was significantly correlated to GA as measured with the barostat on a separate day. The satiety drinking test had a sensitivity and specificity for predicting impaired GA of respectively 92% and 86% (15). In FD patients, the satiety drinking test result was not correlated to sensitivity, to gastric distention or to gastric emptying rate.

The ability of the slow nutrient drink test to assess GA was further supported by its sensitivity to pharmacologically induced impaired GA in HV, by the nitric oxide synthase inhibitor L-NMMA (26) . In addition, acute anxiety in an experimental setting inhibited accommodation and this was associated with increased satiety scores during a satiety drinking test (27) . The same test was used by Cuomo *et al.* in 52 FD patients, who did not study GA, found no relationship with half emptying time or lag time, but found a significant correlation with fractional gastric emptying rate (24). A study from Japan did not confirm the correlation between accommodation as measured with the barostat and nutrient volume tolerance in a slow nutrient drink test, but the study was conducted only in 18 healthy male controls and no patients (22). In a study in 60 FD patients, Van Lelyveld *et al.* found no correlation between GA as measured with the barostat and the outcome of a slow nutrient drink test (28). In a post-hoc analysis of data from HV and FD patients, the Mayo clinic group found no correlation between the slow nutrient drink test and gastric volume changes in response to a fixed meal ingestion of Ensure® as measured with single photon emission computed tomography (SPECT) (29). Measurement of the drop in intragastric pressure during nutrient drink ingestion or intragastric infusion has been proposed as a minimally invasive approach to measuring GA (23, 25, 30, 31). In these studies, a good correlation was found between the drop in intragastric pressure and volume tolerance with a satiety drinking or infusion test (23, 25).

Taken together, these findings suggest that the rapid drink test is mainly a challenge for gastric sensitivity to distention while the satiety drinking test is mainly determined by GA, although not confirmed in all studies. Compared to the gold standard for both of these measures, the gastric barostat, drink tests have several advantages such as their non-invasive nature and easy performance, the documented excellent reproducibility in HV and FD patients, and the very low cost (32, 33). Drink tests require no specific experience and are not user-dependent. There are no limitations in testing obese, pregnant women or other patients and even in testing pediatric patients (19). Disadvantages of the use of a drink test to assess gastric sensitivity is the challenge of (rapid) drinking, which eliminates its use in patients with dysphagia, and, in case a nutrient load is used, palatability of the nutrient. There are also some disadvantages in the use of the drink test as a GA test where it represents at best an indirect measurement of GA. Drawbacks are the subjective nature of the satiety scoring and the susceptibility to sensory and psychological influences. In drink tests, there is the awareness of the amount that has been ingested, especially when drinking consecutive aliquots of 100 ml. This is less the case when the subject is drinking from a dripping peristaltic pump. To overcome awareness of ingested volume and palatability effects, some authors have used intragastric nutrient infusion when assessing GA (23, 30, 31, 33-37).

**Results of drink tests in Gastroparesis**

Relatively few data are available on the use of drink tests focussing specifically on GP. In several studies in FD using drink tests, patients also underwent gastric emptying testing. The outcome of rapid drink tests was not correlated to gastric emptying rate but in the study by Jones *et al.* rapid water volume tolerance was correlated with the lag phase of the emptying test (8, 11). They also reported significantly lower volume tolerance of a rapid water drink test in 19 GP patients compared to controls (11). In a study by the NIDDK Gastroparesis Clinical Research Consortium enrolling 198 GP patients (134 idiopathic, 64 diabetic), increasing severity of early satiety and postprandial fullness were associated with decreased tolerance of the water load test (39). Abdominal pain scores in GP patients from the same cohort were not associated with the water load test (40). Koch et al. studied tolerance of a rapid water drink test and a rapid nutrient drink test in 45 subjects with diabetic gastroparesis (41). Volume tolerance in both tests was comparable and lower than that of historical controls. The nutrient drink test elicited more fullness, bloating and discomfort than the water load test, while the levels of nausea were similar. The use of an insulin pump for 24 weeks did not alter symptoms and water or nutrient load tolerance in these patients (41).

In the original description of the satiety drink test, gastric emptying rate was not significantly correlated to the ingested volume in FD patients (15). In a study in secondary care, both nutrient drink tests and gastric emptying breath tests were performed, and no correlation between both was reported (18).

**Pharmacological modulation of nutrient drink tests**

Nitric oxide (NO) is the main inhibitory neurotransmitter involved in the GA reflex (42). Using the gastric barostat, it was shown that the administration of the selective NO synthase inhibitor, NG-monomethyl -L- Arginine (L-NMMA), at a dose of 6-8 mg/kg/hour, inhibits GA. At the same dose, L-NMMA also decreased liquid meal tolerance in the nutrient drink test (26).

The effect on slow nutrient drink test outcomes was concordant with their effect on GA for several pharmacological agents (Supplemental Figure 1). In HV, administration of sumatriptan and cisapride increased and erythromycin decreased slow nutrient drink test volume tolerance, in line with their effects on gastric accommodation (14, 15, 43, 44). Motilin infusion inhibited gastric accommodation and decreased nutrient volume tolerance in HV (45). Sumatriptan had no effect on volume tolerance of a rapid nutrient drink test (200 ml/min) (46) . Administration of naloxone, a non-selective opioid receptor antagonist in HV, significantly inhibited GA measured with the barostat and decreased satiety drinking test volume tolerance (47). Similar results were obtained after the administration of the peripherally restricted μ-opioid antagonist, methylnaltrexone, in a study in which the GA was assessed using both barostat and HRM. These effects were correlated with a decreased nutrient volume tolerance in a drink test study (48) . The NK1 receptor antagonist aprepitant increased gastric volumes as measured by SPECT, and also increased maximum tolerated nutrient drink test volumes (49). In a nutrient drink test study, healthy subjects reached maximal satiation significantly earlier after treatment with sildenafil, a phosphodiesterase type 5 (PDE5) inhibitor. This finding was concordant with the result of intragastric pressure measurement, showing decreased accommodation, but not with the barostat study results (34).

For a number of other agents, especially with central mechanisms of action, pharmacological effects on the nutrient drink test were reported which did not match with the effects on GA (Supplemental Figure 1). These include the 5-HT3 receptor antagonist ondansetron, which increased tolerance in a satiety drinking test but did not alter GA measured with the barostat (50). The 5-HT4 receptor agonist tegaserod enhanced GA in HV, but did not alter tolerance of Ensure® ingested at a rate of 120 ml every 4 minutes (51, 52). Mosapride and prucalopride, both 5-HT4 receptor agonists, also did not alter volume tolerance of a slow nutrient drink test (22, 53). Acute administration of the selective serotonin reuptake inhibitor citalopram enhanced volume tolerance in a satiety drinking test, while the barostat showed a biphasic response with transient relaxation and smaller postprandial volumes (54). Acute tryptophan depletion, which leads to decreased 5-HT levels, enhanced GA but did not alter nutrient volume tolerance of a satiety drinking test (55). The tricyclic antidepressant amitriptyline did not alter gastric volumes measured with SPECT, and did not change tolerance of a slow nutrient drink test in HV (56). Using a similar trial design with several psychotropic agents, venlafaxine but not buspirone or paroxetine, increased postprandial gastric volumes in health evaluated by SPECT, but none of the agents altered nutrient volume tolerance (57). The kappa opioid agonist asimadoline increased volume tolerance in a slow drinking test, but this was not related to changes in gastric volume measured using SPECT (58). Infusion of ghrelin decreased gastric accommodation as measured with the barostat, but did not affect tolerance of a slow nutrient drink test (59). The ghrelin receptor agonist relamorelin did not alter gastric volumes measured by SPECT and did not alter nutrient tolerance measured by drinking 120 ml Ensure® every 4 minutes (60).

To conclude, drink tests have been used in many clinical trials. The most consistent finding has been the link between outcome of the satiety drinking test for agents that alter GA, but this is only consistent for agents without central mode of action.

**Prediction of response to therapy**

Very few studies evaluated the ability of a drink test to predict response to therapy. In a phase 2 study in the United States, FD patients with normal endoscopy were administered a 2-week single blind lansoprazole treatment and the non-responders were randomized to placebo (n=104) or acotiamide 300mg (n=103), 600mg (n=105) and 900mg (n=104) t.i.d in a double-blind fashion for 12 weeks (61) . During the screening period, a slow liquid nutrient drink test to determine maximum tolerated volume (MTV) was performed. Impaired nutrient tolerance (MTV<850 ml), present in 315 patients (81%), was associated with a higher overall (adequate) relief of stomach symptoms during the first four weeks of treatment (27.8 vs. 38.9%, placebo and 300 mg for normal nutrient tolerance; 27.3 vs. 58.4%, placebo vs. 300 mg in impaired nutrient tolerance, p < 0.01) (62).

In a placebo-controlled study in 40 FD patients, asimadoline at doses of 0.5 or 1.0 mg b.i.d. did not alter nutrient volume tolerance and symptoms (63) . In a controlled study, amitriptyline improved symptoms in FD, whereas escitalopram had no effect over placebo (64). In a mechanistic substudy, both amitriptyline and escitalopram enhanced gastric accommodation but had no influence on nutrient volume tolerance, measured by drinking 120 ml Ensure® every 4 minutes (65).

In GP patients, the NORIG study, nortriptyline was equal to placebo in improving symptoms in idiopathic gastroparesis, and the tolerance of a graded nutrient liquid drink test was also not altered (66). TAK-906, a novel dopamine-2 receptor antagonist, was evaluated at doses of 0, 5, 25 and 100 mg in a phase 2 study in gastroparesis. The intermediate dose (25 mg) gave the best symptom improvement, and this was matched by improved nutrient drink test tolerance (67).

While there are early encouraging outcomes, to the application of a drink test as a predictive biomarker for treatment outcome deservers further studies in upcoming phase 2 pharmacological trials. Preferably, this is done after standardization of the methodology in terms of speed of nutrient administration and choice of type of nutrient.

**FIGURE LEGENDS**

**Supplemental Figure 1.** Overview of the effect of several pharmacological agents on the nutrient drink test, and their concordance (right side of the figure) or lack of concordance (left side of the figure) with effects on gastric accommodation. Each box indicates the effect on gastric accommodation (GA) and on drink tolerance (DT). Behind each individual agent, the method used for measuring GA (GB = gastric barostat; SPECT = single photon emission computed tomography; HRM = high resolution manometry) and the type of drink test (SNDT = slow nutrient drink test; SatT = satiety drinking test) is specified between brackets.

**References:**

8. Boeckxstaens GE, Hirsch DP, Van Den Elzen BD, et al. Impaired drinking capacity in patients with functional dyspepsia: relationship with proximal stomach function. Gastroenterology 2001;121:1054-1063.

9. Strid H, Norström M, Sjöberg J, et al. Impact of sex and psychological factors on the water loading test in functional dyspepsia. Scandinavian journal of gastroenterology 2001;36:725-730.

10. Abid S, Anis MK, Azam Z, et al. Satiety drinking tests: Effects of caloric content, drinking rate, gender, age, and body mass index. Scandinavian journal of gastroenterology 2009;44:551-556.

11. Jones MP, Hoffman S, Shah D, et al. The water load test: observations from healthy controls and patients with functional dyspepsia. American Journal of Physiology-Gastrointestinal and Liver Physiology 2003;284:G896-G904.

12. Hjelland I, Ofstad A, Narvestad J, et al. Drink tests in functional dyspepsia: which drink is best? Scandinavian journal of gastroenterology 2004;39:933-937.

14. Tack J, Broeckaert D, Coulie B, et al. The influence of cisapride on gastric tone and the perception of gastric distension. Alimentary pharmacology & therapeutics 1998;12:761-766.

14. Tack J, Piessevaux H, Coulie B, et al. Role of impaired gastric accommodation to a meal in functional dyspepsia. Gastroenterology 1998;115:1346-1352.

15. Tack J, Caenepeel P, Piessevaux H, et al. Assessment of meal induced gastric accommodation by a satiety drinking test in health and in severe functional dyspepsia. Gut 2003;52:1271-1277.

18. Kindt S, Coulie B, Wajs E, et al. Reproducibility and symptomatic predictors of a slow nutrient drinking test in health and in functional dyspepsia. Neurogastroenterology & Motility 2008;20:320-329.

19. Hoffman I, Vos R, Tack J. Normal values for the satiety drinking test in healthy children between 5 and 15 years. Neurogastroenterology & Motility 2009;21:517-e6.

22. Iida A, Konagaya T, Kaneko H, et al. Usefulness of a slow nutrient drinking test for evaluating gastric perception and accommodation. Digestion 2011;84:253-260.

23. Carbone F, Goelen N, Porters K, et al. Impaired Gastric Distribution of a Meal is Associated with Impaired Intragastric Pressure Measurement and Satiation In FD. Gastroenterology 2017;152:S304.

24. Cuomo R, Sarnelli G, Grasso R, et al. Functional dyspepsia symptoms, gastric emptying and satiety provocative test: analysis of relationships. Scandinavian journal of gastroenterology 2001;36:1030-1036.

25. Janssen P, Tack JF. Intragastric pressure (IGP) during intragastric nutrient drink infusion: a method to objectively discriminate functional dyspeptic (FD) patients with impaired nutrient tolerance and/or gastric accommodation. Gastroenterology 2011;140:S-883-S-884.

26. Tack J, Demedts I, Meulemans A, et al. Role of nitric oxide in the gastric accommodation reflex and in meal induced satiety in humans. Gut 2002;51:219-224.

27. Geeraerts B, Vandenberghe J, Van Oudenhove L, et al. Influence of experimentally induced anxiety on gastric sensorimotor function in humans. Gastroenterology 2005;129:1437-1444.

28. van Lelyveld N, Schipper M, Samsom M. Lack of relationship between chronic upper abdominal symptoms and gastric function in functional dyspepsia. Digestive diseases and sciences 2008;53:1223-1230.

29. Gonenne J, Castillo E, Camilleri M, et al. Does the nutrient drink test accurately predict postprandial gastric volume in health and community dyspepsia? Neurogastroenterology & Motility 2005;17:44-50.

30. Carbone F, Tack J, Hoffman I. The intragastric pressure measurement: a novel method to assess gastric accommodation in functional dyspepsia children. Journal of pediatric gastroenterology and nutrition 2017;64:918-924.

31. Janssen P, Verschueren S, Giao Ly H, et al. Intragastric pressure during food intake: a physiological and minimally invasive method to assess gastric accommodation. Neurogastroenterology & Motility 2011;23:316-e154.

32. Kindt S, Tack J. Impaired gastric accommodation and its role in dyspepsia. Gut 2006;55:1685-1691.

33. Mimidis K. Drinking tests in functional dyspepsia: what do they really measure? Neurogastroenterology & Motility 2007;19:947-950.

34. Carbone F, Tack J. The effect of sildenafil on gastric motility and satiation in healthy controls. United European gastroenterology journal 2018;6:846-854.

35. Carbone F, Vanuytsel T, Tack J. The effect of mirtazapine on gastric accommodation, gastric sensitivity to distention, and nutrient tolerance in healthy subjects. Neurogastroenterology & Motility 2017;29:e13146.

36. Masuy I, Carbone F, Holvoet L, et al. The effect of rikkunshito on gastrointestinal symptoms and gastric motor function: The first study in a Belgian functional dyspepsia population. Neurogastroenterology & Motility 2020;32:e13739.

37. Masuy I, Tack J, Verbeke K, et al. Acotiamide affects antral motility, but has no effect on fundic motility, gastric emptying or symptom perception in healthy participants. Neurogastroenterology & Motility 2019;31:e13540.

39. Parkman HP, Hallinan EK, Hasler WL, et al. Early satiety and postprandial fullness in gastroparesis correlate with gastroparesis severity, gastric emptying, and water load testing. Neurogastroenterology & Motility 2017;29:e12981.

40. Parkman HP, Wilson LA, Hasler WL, et al. Abdominal pain in patients with gastroparesis: associations with gastroparesis symptoms, etiology of gastroparesis, gastric emptying, somatization, and quality of life. Digestive diseases and sciences 2019;64:2242-2255.

41. Koch KL, Hasler WL, Van Natta M, et al. Satiety testing in diabetic gastroparesis: Effects of insulin pump therapy with continuous glucose monitoring on upper gastrointestinal symptoms and gastric myoelectrical activity. Neurogastroenterology & Motility 2020;32:e13720.

42. Desai K, Sessa W, Vane J. Involvement of nitric oxide in the reflex relaxation of the stomach to accommodate food or fluid. Nature 1991;351:477-479.

43. des Varannes SB, Parys V, Ropert A, et al. Erythromycin enhances fasting and postprandial proximal gastric tone in humans. Gastroenterology 1995;109:32-39.

45. Cuomo R, Vandaele P, Coulie B, et al. Influence of motilin on gastric fundus tone and on meal-induced satiety in man: role of cholinergic pathways. American Journal of Gastroenterology 2006;101:804-811.

46. Boeckxstaens G, Hirsch D, Kuiken S, et al. The proximal stomach and postprandial symptoms in functional dyspeptics. The American journal of gastroenterology 2002;97:40-48.

47. Geeraerts B, Mimidis K, Van Oudenhove L, et al. Role of endogenous opioids in the control of gastric sensorimotor function. Neurogastroenterology & Motility 2008;20:1094-1102.

48. Janssen P, Pottel H, Vos R, et al. Endogenously released opioids mediate meal‐induced gastric relaxation via peripheral mu‐opioid receptors. Alimentary pharmacology & therapeutics 2011;33:607-614.

49. Jacob D, Busciglio I, Burton D, et al. Effects of NK1 receptors on gastric motor functions and satiation in healthy humans: results from a controlled trial with the NK1 antagonist aprepitant. American Journal of Physiology-Gastrointestinal and Liver Physiology 2017;313:G505-G510.

51. Tack J, Vos R, Janssens J, et al. Influence of tegaserod on proximal gastric tone and on the perception of gastric distension. Alimentary pharmacology & therapeutics 2003;18:1031-1037.

52. Talley N, Camilleri M, Burton D, et al. Double‐blind, randomized, placebo‐controlled study to evaluate the effects of tegaserod on gastric motor, sensory and myoelectric function in healthy volunteers. Alimentary pharmacology & therapeutics 2006;24:859-867.

53. Carbone F, Tack J. The effect of prucalopride on gastric accommodation in healthy volunteers. Neurogastroenterology and Motility 2014;26:3-4.

54. Janssen P, Van Oudenhove L, Casteels C, et al. The effects of acute citalopram dosing on gastric motor function and nutrient tolerance in healthy volunteers. Alimentary pharmacology & therapeutics 2011;33:395-402.

50. Janssen P, Vos R, Van Oudenhove L, et al. Influence of the 5‐HT3 receptor antagonist ondansetron on gastric sensorimotor function and nutrient tolerance in healthy volunteers. Neurogastroenterology & Motility 2011;23:444-e175.

55. Geeraerts B, Van Oudenhove L, Boesmans W, et al. Influence of acute tryptophan depletion on gastric sensorimotor function in humans. American Journal of Physiology-Gastrointestinal and Liver Physiology 2011;300:G228-G235.

56. Bouras EP, Talley NJ, Camilleri M, et al. Effects of amitriptyline on gastric sensorimotor function and postprandial symptoms in healthy individuals: a randomized, double-blind, placebo-controlled trial. The American journal of gastroenterology 2008;103:2043.

57. Chial HJ, Camilleri M, Burton D, et al. Selective effects of serotonergic psychoactive agents on gastrointestinal functions in health. American Journal of Physiology-Gastrointestinal and Liver Physiology 2003;284:G130-G137.

58. Delgado‐Aros S, Chial H, Cremonini F, et al. Effects of asimadoline, a κ‐opioid agonist, on satiation and postprandial symptoms in health. Alimentary pharmacology & therapeutics 2003;18:507-514.

59. Ang D, Nicolai H, Vos R, et al. Influence of ghrelin on the gastric accommodation reflex and on meal‐induced satiety in man. Neurogastroenterology & Motility 2009;21:528-e9.

60. Nelson AD, Camilleri M, Acosta A, et al. Effects of ghrelin receptor agonist, relamorelin, on gastric motor functions and satiation in healthy volunteers. Neurogastroenterology & Motility 2016;28:1705-1713.

63. Talley N, Choung R, Camilleri M, et al. Asimadoline, a kappa‐opioid agonist, and satiation in functional dyspepsia. Alimentary pharmacology & therapeutics 2008;27:1122-1131.

64. Talley NJ, Locke GR, Saito YA, et al. Effect of amitriptyline and escitalopram on functional dyspepsia: a multicenter, randomized controlled study. Gastroenterology 2015;149:340-349. e2.

65. Lacy B, Saito Y, Camilleri M, et al. Effects of antidepressants on gastric function in patients with functional dyspepsia. American Journal of Gastroenterology 2018;113:216-224.

66. Parkman HP, Van Natta ML, Abell TL, et al. Effect of nortriptyline on symptoms of idiopathic gastroparesis: the NORIG randomized clinical trial. Jama 2013;310:2640-2649.

67. Dukes G, Scimia C, Kuo B, et al. Safety, tolerability and pharmacodynamics of TAK-906, a dopamine 2, 3 antagonist, in patients with diabetic or idiopathic gastroparesis. In: Neurogastroenterology and Motility; 2019. WILEY 111 RIVER ST, HOBOKEN 07030-5774, NJ USA; 2019.

62. Tack JF, Talley NJ, Kowalski DL, et al. 963 Influence of PPI Run-in, pH Monitoring and Nutrient Tolerance On Efficacy Outcomes of Acotiamide Hydrochloride (YM443), a Novel Acetylcholine Esterase Inhibitor, in Functional Dyspepsia. Gastroenterology 2008;134:A-143.

61. Talley NJ, Tack JF, Kowalski DL, et al. 1053 a novel acetylcholine esterase inhibitor Acotiamide hydrochloride (YM443) in functional dyspepsia: efficacy in a randomized, double-blind, placebo-controlled dose ranging trial. Gastroenterology 2008;134:A-157-A-158.