HHS Public Access

Author manuscript

Clin Gastroenterol Hepatol. Author manuscript; available in PMC 2017 August 01.

Published in final edited form as:

Clin Gastroenterol Hepatol. 2016 August ; 14(8): 1072–1080. doi:10.1016/j.cgh.2015.12.033.

Novel Diet, Drugs and Gastric Interventions for Gastroparesis

Michael Camilleri, M.D.

Clinical Enteric Neuroscience Translational and Epidemiological Research (C.E.N.T.E.R.), Mayo Clinic, Rochester, Minnesota

Abstract

This review of the pathophysiological basis for gastroparesis and recent advances in the treatment of patients with gastroparesis shows that there are several novel approaches to advance treatment of gastroparesis including diet, novel prokinetics, interventions on the pylorus, and novel forms of gastric electrical stimulation. The field of gastroparesis is likely to advance with further studies, with the help from a guidance document from the FDA on gastroparesis, and with the recent approval of the stable isotope gastric emptying test to ensure eligibility of participants in multicenter trials. Clinical experience and a formal, randomized, controlled trial provide insights on optimizing dietary interventions in patients with gastroparesis. This review addresses the biological rationale of these different treatments, based on known physiology and pathophysiology of gastric emptying. The novel medications include the motilin agonist, camicinal, 5-HT_4 receptor agonists such as velusetrag, and the ghrelin agonist, relamorelin. New approaches target pylorospasm by either stent placement, endoscopic pyloric myotomy or laparoscopic pyloroplasty. These approaches offer the opportunity to achieve more permanent reduction of resistance to flow at the pylorus over the intrapyloric injection of botulinum toxin, which typically has to be repeated every few months if it is efficacious. A novel device, deployed in porcine stomach, involved per-endoscopic electrical stimulation. These promising approaches require formal, randomized, controlled trials and deployment in patients. The presence of concomitant antral hypomotility may be a significant factor in the responsiveness to interventions at the pylorus.

Keywords

gastric emptying; motility; pylorus; myotomy; stent; prokinetics; diet

Corresponding author: Michael Camilleri, M.D., Mayo Clinic, Charlton 8-110, 200 First St. S.W. Rochester, MN 55905, camilleri.michael@mayo.edu, Tele: 507-266-2305.

Author's contributions: literature review, and drafting and revision of the manuscript

Disclosures: The author has no financial or personal relationships that could present a potential conflict of interest.

Introduction: Physiological Basis for Emptying of Food from the Stomach

Gastric Emptying of Solids and Liquids

Different meals are emptied at different rates, based on the physical consistency,[1] fat content and total caloric load. This is well illustrated by the emptying profiles of different meals in Figure 1.[2] In general, liquids of low caloric density empty under the pressure gradient between fundic tone and pylorus and little motor action of the distal stomach, and liquids empty exponentially from the stomach. Higher caloric liquids or homogenized solids empty almost linearly under the pressure gradient from the fundus and coordinated antropyloroduodenal motility. Digestible food of more solid consistency requires antral trituration until the particle size is reduced to <2mm;[3] after trituration occurs, food empties linearly from the stomach at a rate similar to that of a homogenized solid meal. Trituration involves establishing liquid shearing forces where solids and liquids are repeatedly propelled against a closed pylorus at the maximum frequency of three times per minute in humans. Until particles are reduced by these forces to <2mm, there is a lag before emptying can start. Thus, gastric emptying occurs in two periods: the lag period and the post-lag, linear emptying period.[4,5] Non-digestible solids are usually emptied from the stomach with the interdigestive migrating motor complex (MMC).[1] Since about one-third of MMCs, even in healthy humans, may not be associated with an antral component[6] and since there is a wide range in the number of MMCs per day,[7] it is possible for non-digestible solids to remain in the stomach for several hours, even in healthy stomachs. The clinical relevance of this physiological principle is that the finding of residual non-digestible food in the stomach at endoscopy after overnight fasting is not necessarily pathological.

Definition of Gastroparesis

Gastroparesis is a syndrome of significantly delayed gastric emptying in the absence of mechanical obstruction and cardinal symptoms that include early satiety, postprandial fullness, nausea, vomiting, bloating and upper abdominal pain.[8] Diabetes, postsurgical, idiopathic or post-viral gastroparesis are the most common associated conditions; more rarely, gastroparesis is associated with other conditions such as extrinsic neurological disorders including Parkinsonism, paraneoplastic disease and scleroderma.[9]

Motor Mechanisms Deranged in Gastroparesis

In gastroparesis, there is an abnormal function of smooth muscle, enteric and extrinsic autonomic nerves, or the interstitial cells of Cajal (pacemakers in the stomach wall). However, the pathophysiological disturbances in these conditions resulting from diverse pathological mechanisms appear to be uniform.[10] Myopathic disorders are typically infiltrative diseases such as scleroderma or amyloidosis, degenerative disorders such as hollow visceral myopathy, or mitochondrial cytopathy. When these disorders cause gastroparesis, they invariably present as a more generalized motility disorder affecting other regions such as the small bowel, esophagus and lower esophageal sphincter.[11]

Gastric emptying delay in gastroparesis is associated with distal antral hypomotility, pylorospasm or intestinal dysmotility.[12,13] Measurement of gastric emptying does not differentiate neuropathic from myopathic disorders;[11] the distinction requires appraisal for

systemic, serologic or biopsy manifestations of the underlying diseases (such as features of scleroderma or mitochondrial cytopathy, serum and urine protein electrophoresis, fat or duodenal biopsy for amyloidosis) or, rarely, documentation of low amplitude esophageal (typically <30mmHg),[14] lower esophageal resting pressure (typically <20mmHg),[15,16] antral (typically <40mmHg) or duodenal (typically <10mmHg) contraction amplitude by manometry.[11,17,18]

In general, antral hypomoility is usually present when there is pylorospasm (Figure 2).[19] This phenomenon is also observed under experimental conditions, such as when saline is replaced by hypertonic glucose in the liquid phase of the meal, or by the addition of high concentration of lipid by intraduodenal infusion.[20,21]

Decreased postprandial antral motility index prolongs the gastric emptying time for solids by prolonging the lag duration and lowering the rate of post-lag emptying;[13] intestinal dysmotility retards the gastric emptying rate, typically without prolonging lag phase of gastric emptying (Table 1). Finding residual food in the stomach at the time of endoscopy after a period of fasting may occur in patients with gastroparesis.

Novel Diagnostics Approved for Gastroparesis

Gastric emptying by scintigraphy (details in Supplementary Material) is still widely used.[22–24] Recently, the Food and Drug Administration (FDA)[25] approved the wireless motility capsule which detects gastric emptying time at the point of care by identifying the sudden change in pH from entry into the duodenum,[26] and a stable isotope test to evaluate gastric emptying noninvasively without radiation hazard. ^{13}C isotope is incorporated into a solid meal by growing the blue-green algae, *Spirulina platensis*, in $13CO_2$-enriched chambers. After being emptied from the stomach, the *S. platensis* is digested and absorbed in the proximal small intestine, metabolized by the liver, and excreted by the lungs, resulting in a rise in expired $^{13}CO_2$ over baseline. This test assumes that the rate limiting step in $^{13}CO_2$ excretion is gastric emptying of the labeled test meal, and may be inaccurate in conditions associated with significant malabsorption, liver or lung diseases. The test was evaluated with simultaneous scintigraphy in 38 healthy volunteers and 129 patients with suspicion of delayed gastric emptying.[27,28] At 80% specificity, there was 89% sensitivity to correctly predict the gastric emptying category using breath test metrics compared to simultaneous scintigraphy. In addition, the gastric emptying breath test results agreed with scintigraphy 73–97% of the time, when measured at various time points during the test.[26]

Advances in Dietary Recommendations

Based on observations in their vast clinical experience, Parkman and colleagues have reported the foods that provoke symptoms and those that were tolerated by patients with gastroparesis. A study of 45 patients identified that foods provoking symptoms, such as orange juice, fried chicken, cabbage, oranges, sausage, pizza, peppers, onions, tomato juice, lettuce, coffee, salsa, broccoli, bacon, and roast beef, were generally fatty, acidic, spicy, and roughage-based.[29] A high-fat solid meal significantly increased overall symptoms among individuals with gastroparesis.[30] On the other hand, saltine crackers, jello, and graham

crackers moderately improved symptoms, and 12 additional foods were tolerated without provoking symptoms. These were: ginger ale, gluten-free foods, tea, sweet potatoes, pretzels, white fish, clear soup, salmon, potatoes, white rice, popsicles, and applesauce.[29]

Over the past three decades, patients have received dietary advice based on physiological principles rather than evidence. However, a randomized, controlled trial has demonstrated that a small particle size diet reduces upper gastrointestinal symptoms (nausea, vomiting, bloating, postprandial fullness, regurgitation and heartburn) in patients with diabetic gastroparesis.[31]

Current Medications and Novel Insights on their Use

Currently approved drugs for treatment of gastroparesis target dopamine D_2 receptors; metoclopramide (a D_2-receptor antagonist with some 5-HT_4 receptor agonism) is the only FDA-approved medication for the treatment of gastroparesis, and the recommendation is that treatment should be for no longer than 12 weeks. Domperidone is also a dopamine D_2 receptor antagonist that can be prescribed through the FDA's expanded access to investigational drugs. Metoclopramide received a black box warning from FDA because of the risk of tardive dyskinesia, although the actual prevalence of involuntary movements and especially tardive dyskinesia was probably overestimated, as discussed in detail elsewhere.[32] A novel preparation of metoclopramide is in the form of nasal spray, which reduced symptoms of gastroparesis in women, but not in men, in a multicenter, double-blind study of 285 subjects (71% female) with type 1 or type 2 diabetes and a previous diagnosis of gastroparesis with diabetes.[33]

Domperidone is associated with risk of sudden cardiac death based on evidence from case-control studies,[34] particularly at higher systemic concentrations of the drug and especially in patients with a higher baseline risk of QT prolongation,[35] and has restricted use in Europe.

Macrolide antibiotics are agonists at motilin receptors. Although not approved for gastroparesis, erythromycin and azithromycin are often used in practice, based on efficacy in the short term and similar efficacy in ameliorating gastric emptying[36] and antral pressure activity.[37] They improve gastric emptying, but are associated with tachyphylaxis[38] due to down regulation of the motilin receptor, which typically starts after two weeks of the onset of therapy.[39] Clarithromycin reduced symptoms in patients with *H. pylori* non-ulcer dyspepsia and enhanced upper gastrointestinal motility,[40] but it did not accelerate gastric emptying.[41]

Co-administration of anti-emetics and prokinetics may result in drug interactions because of induction or inhibition of cytochrome P450 enzymes involved in drug metabolism, potentially causing high blood levels and drug toxicity.[42] Erythromycin is extensively metabolized by cytochrome P450 CYP3A. Many commonly used medications inhibit the effects of CYP3A (reviewed elsewhere[43]) and may increase plasma erythromycin concentrations, increasing the risk of ventricular arrhythmias and sudden death.[44]

A large NIH-funded gastroparesis consortium trial attempted to relieve symptoms of gastroparesis by altering visceral sensitivity with nortriptyline, but proved to be not efficacious.[45]

In summary, there continues to be a significant unmet need for patients with gastroparesis, requiring prescribers of current medications to balance attempts to relieve patients' symptoms with the potential for litigation, in view of the FDA black box warning on risk of tardive dyskinesia and the admonition to prescribe the only approved drug for gastroparesis for only three months, despite evidence the disease may persist over 25 years.[46]

New Medications

Novel Motilin Agonist

Tachyphylaxis and the propensity for drug interactions point toward a need for a more selective motilin receptor agonist. A novel pharmacological approach has significant promise, based on the theoretical ability to induce the motilin receptors to preferentially ('biased agonism') activate the β-arrestin pathway, enhancing the ability to more quickly recover from desensitization of the receptor.[47] GSK962040 (or camicinal) is such a small molecule, selective motilin receptor agonist. It was shown to induce phasic contractions and increase gastrointestinal motility in conscious dogs,[48] preferentially mediating cholinergic activity in the antrum relative to the fundus and the small intestine.[49] Results from a phase II, 4-week clinical study in type 1 and type 2 diabetic gastroparesis are eagerly awaited (ClinicalTrials.gov NCT01262898).

Ghrelin Agonist

Relamorelin (RM-131) is a pentapeptide ghrelin receptor agonist that reversed postsurgical gastric ileus or delayed gastric emptying in rats and in healthy primates. Prokinetic efficacy in models of gastrointestinal disorders in rats showed relamorelin to be 600- to 1800-fold more potent compared to other ghrelin mimetics in increasing gastric emptying.[50]

Relamorelin accelerated gastric half-emptying time of solids in patients with type 2 or type 1 diabetes who had prior documentation of delayed gastric emptying.[51,52] In a phase II study of 4 weeks duration in type 1 diabetic patients, relamorelin also accelerated gastric emptying and reduced upper gastrointestinal symptoms in patients with high baseline vomiting.[53]

New 5-HT_4 Receptor Agonists

In the past, the lack of selectivity of 5-HT_4 receptor agonists such as cisapride, which was widely used for upper gastrointestinal indications, was associated with rare cardiac dysrhythmias due to effects on ion channels [delayed rectifier potassium (IKr) channel] in cardiac muscle. New prokinetic agents currently under investigation have greater selectivity and specificity for 5-HT_4 receptors in the gastrointestinal tract than for the IKr channel and have less intrinsic activity on cardiac muscle.[54] In a preliminary study, Carbone et al. have demonstrated efficacy of prucalopride in gastroparesis.[55]

Velusetrag is a selective 5-HT_4 receptor agonist. In the past, velusetrag (15, 30 or 50mg daily) administered to patients with chronic idiopathic constipation for 4 weeks was well

tolerated,[56] and accelerated gastric emptying after 4–9 days of treatment;[57] it is now undergoing clinical trials in patients with gastroparesis (ClinicalTrials.gov Identifier: NCT02267525).

YKP10811 is a novel benzamide derivative, selective 5-HT_4 receptor agonist. In patients with functional constipation, 10 and 20mg doses accelerated gastric emptying, on per-protocol analysis, and orocecal transit. No significant adverse events were reported.[58]

Pyloric Interventions

The rationale for interventions on the pylorus is based on the observation of pylorospasm in patients with gastroparesis or experimental conditions associated with delayed gastric emptying, such as the intraduodenal injection of lipid. There is reduced expression of neuronal nitric oxide synthase in pylorus of non-obese diabetic mice when they develop diabetes,; the reduced expression is reversed by insulin treatment.[59] In this model, the gastric emptying delay in both non-obese diabetic and streptozotocin diabetic mice was reversed with the phosphodiesterase 5 inhibitor, sildenafil (which increases intracellular cGMP and mimics the effect of nitric oxide). Unfortunately, sildenafil had no significant effect on gastric emptying in gastroparesis associated with uremia.[60]

Intrapyloric Injection of Botulinum Toxin

There is good experimental rationale for considering intrapyloric injection of botulinum toxin as treatment for pylorospasm. Thus, botulinum toxin directly inhibits smooth muscle contractility, as evidenced by a decreased contractile response to acetyl choline.[61]

Based on the results of the randomized, controlled trials comparing botulinum toxin to sham/placebo injection,[62,63] a guideline on gastroparesis did not recommended intrapyloric injection of botulinum toxin for patients with gastroparesis.[64] On the other hand, small observational studies suggested that intrapyloric botulinum toxin can improve both gastric emptying and symptoms,[65–69] and a retrospective, single-center, open-label study of 179 patients reported decreased symptoms of gastroparesis 1 to 4 months after intrapyloric botulinum toxin in 51.4% of patients, with greater benefit observed with a 200-unit compared to a 100-unit dose, female gender, age <50 years, and idiopathic gastroparesis; moreover, a clinical response to a second injection was observed in 73.4% of evaluable patients.[70]

This experience has led to testing other interventions on the pylorus to try to treat gastroparesis.

Endoscopic Placement of a Transpyloric Stent

The endoscopic placement of a through-the-scope, double-layered, fully-covered Niti-S self-expandable metal transpyloric stent, which is anchored by suturing on the gastric side, has been tested in small, open-label studies, typically in patients with refractory gastroparesis.[71,72] A guidewire is advanced into the distal duodenum, and the self-expandable metal stent delivery system is placed over the guidewire. The stent is deployed under endoscopic visualization, such that the proximal flared end is in the antrum and the

distal flared end in the duodenum proximal to the duodenal papilla. Technical success was achieved during 98% of procedures. Best results (with no stent migration) during mean follow-up of 146 days were obtained when the stent was anchored with endoscopic suturing, though even that group had 52% stent migration.

Although data are incomplete, there were improvements in gastric emptying and clinical outcomes in 75% of patients with adequate follow-up, with greater efficacy in those with predominant nausea and/or vomiting (79% response) rather than those with predominant pain (21% response).

Laparoscopic Pyloroplasty

Prior literature had documented that pyloroplasty may relieve symptoms in gastroparesis and is often combined with operative jejunal tube placement to support nutrition.[73,74] Recently, laparoscopic pyloroplasty was evaluated in a retrospective study of 46 patients: gastric emptying normalized in 60%, and the Gastroparesis Cardinal Symptom Index showed statistically significant reduction in symptom severity for all nine categories, as well as total symptom score.[75]

Gastric Per-Oral Endoscopic Myotomy

Individual case reports of endoscopic pyloromyotomy (G-POEM or gastric per-oral endoscopic myotomy) have been reported from the United States[76] and Europe,[77] and the experience has been extended to include patients with gastroparesis secondary to vagal injury.[78]

In 7 patients[79] with idiopathic (n=5) or post-surgical (n=2) gastroparesis, G-POEM was performed under laparoscopic guidance, as the patients also required concurrent laparoscopic cholecystectomy or fundoplication. Within 30 days of the procedure, one patient had bleeding from a 1cm pyloric channel ulcer with an exposed vessel that was clipped, and within 60 days, one patient had mild pancreatitis thought to be unrelated. At average patient follow up of 6.5 months (range 2–11 months), 6 of 7 patients reported improvement of nausea and epigastric burning, but not of vomiting, early satiety, postprandial fullness or pain. The seventh patient went on to laparoscopic pyloroplasty. In the 5 of 7 patients with follow up gastric emptying data, the mean t1/2 gastric emptying of solids decreased from 124 minutes to 58 minutes (p=0.018).

Appraisal of Pyloric Interventions, Novel Medications, Devices and Surgical Approaches

Randomized sham- or placebo-controlled trials are required to establish the role of these approaches in patients with gastroparesis. Their success may be influenced by concomitant antral hypomotility. Addition of an effective and safe prokinetic that stimulates antral motor function may be beneficial.

Gastric Electrical Stimulation

In the United States, the gastric electrical neurostimulator (Enterra Therapy System®, Medtronic, Inc, Minneapolis, MN) has been approved as a humanitarian exemption device

for diabetic and idiopathic gastroparesis,[80] typically in those with persistence of symptoms despite antiemetic and prokinetic drug therapy for at least one year. A guideline on gastroparesis recommended that gastric electrical stimulation may be considered for compassionate treatment in patients with refractory symptoms, particularly nausea and vomiting. Symptom severity and gastric emptying have been shown to improve in patients with diabetic gastroparesis, but not in patients with idiopathic or postsurgical gastroparesis (conditional recommendation, moderate level of evidence).[64] The National Institute of Health and Care Excellence issued guidelines in 2014 stating that current evidence is adequate to support the use of gastric electrical stimulation.[81]

Since that recommendation, effectiveness in clinical practice was reported in 151 patients from a single center; at mean 1.4 years of follow up, 43% reported at least moderately improved symptoms.[82] Recently, efforts have focused on endoscopic deployment of the gastric stimulator.

Endoscopic Gastric Stimulator Implantation

Temporary gastric stimulators placed endoscopically have been used to determine response to gastric electrical stimulation before permanent implantation through a surgical approach;[83,84] however, there was no permanent endoscopic approach possible until recently. Deb et al.[85] developed a novel, wirelessly powered miniature gastric electrical stimulation device implanted into the pig stomach through an over-tube and attached to the gastric mucosa with endoclips.[86] Electrogastrogram recordings have demonstrated more consistent gastric slow wave amplitudes compared to with no stimulation. The method still needs to be deployed and validated in humans.

FDA Draft Guidance for Clinical Evaluation of Drugs for Treatment of Gastroparesis

The FDA has issued recommendations regarding trial design, trial populations, outcome assessment measures, and trial endpoints for gastroparesis.[87] The following summarizes the draft guidance which is currently open for comments:

1. *Trial design* generally should consist of a randomized, double-blind, placebo- controlled trial and should include a 1- to 2-week screening period.
2. *Treatment period* of at least 12 weeks' duration, followed by a 2- to 4-week randomized withdrawal period, to address the need for maintenance treatment to prevent sign or symptom recurrence.
3. *Daily diaries* should be collected throughout the entire study. In addition, a placebo- controlled, long-term safety study of 12 months' duration, with appropriate pre-specified provisions for rescue medications, should be performed.

4. *Idiopathic and diabetic* gastroparesis patients should be studied in *separate trials*; diabetic gastroparesis patients should have controlled and stable blood glucose levels, and patients on opioids should be excluded.

5. Outcome should be assessed with *patient response outcomes* (PRO) for five core signs and symptoms of gastroparesis — nausea, vomiting, early satiety, abdominal pain, and postprandial fullness. Further validation in well-controlled clinical trials was recommended.

6. PRO measure of *signs and symptoms of gastroparesis* should form the basis of the *primary efficacy assessment* in therapeutic trials for diabetic and idiopathic gastroparesis, with primary endpoint measuring change in signs and symptoms from baseline.

7. Definition of clinically meaningful changes in sign and symptom scores using a *global measure*: "How would you rate your overall severity of gastroparesis signs and symptoms over the past 30 days?" Responses would range from 0=no signs and symptoms; 1=mild; 2=moderate; 3=severe; and 4=very severe.

It is important to note that Revicki et al.[88,89] have extensively validated a daily diary for measurement of gastroparesis signs and symptoms as recommended by the FDA.

Conclusion

There are several novel approaches to advance treatment of gastroparesis. The field is likely to advance with the helpful guidance document from the FDA on gastroparesis,[87] the recent approval of stable isotope gastric emptying test to ensure eligibility of participants in multicenter trials,[26] and the validation of patient response outcomes for trials in gastroparesis based on daily diaries.[88,89]

Acknowledgments

Grant support: Dr. M. Camilleri is funded by grant R01-DK67071 from National Institutes of Health.

Abbreviations used

MMC migrating motor complex

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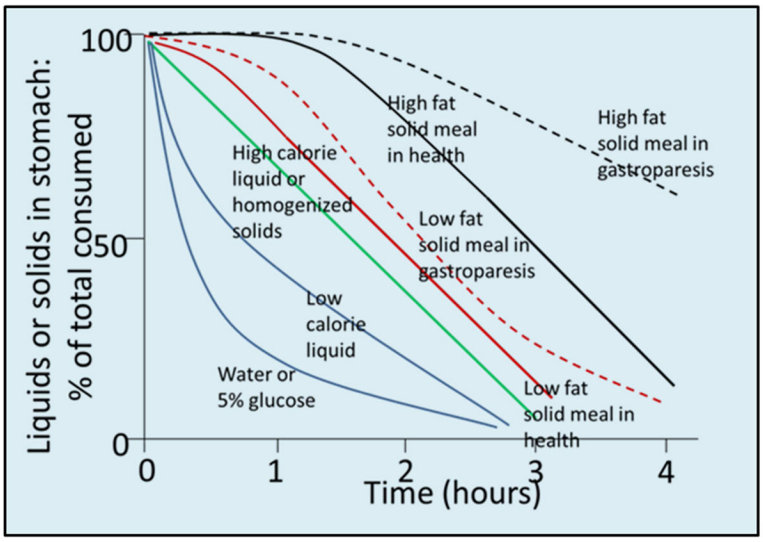

Figure 1.

Patterns of gastric emptying of liquids and solids in health and in gastroparesis. Gastric emptying curves for liquids and solids were derived from the published literature. Low fat solid meal is a 2% fat, 255kcal meal; high fat meal is 32% fat, 296kcal meal. Reproduced with permission from ref. 2. Camilleri M, Shin A. Dig Dis Sci 2013;58:1813–1815.

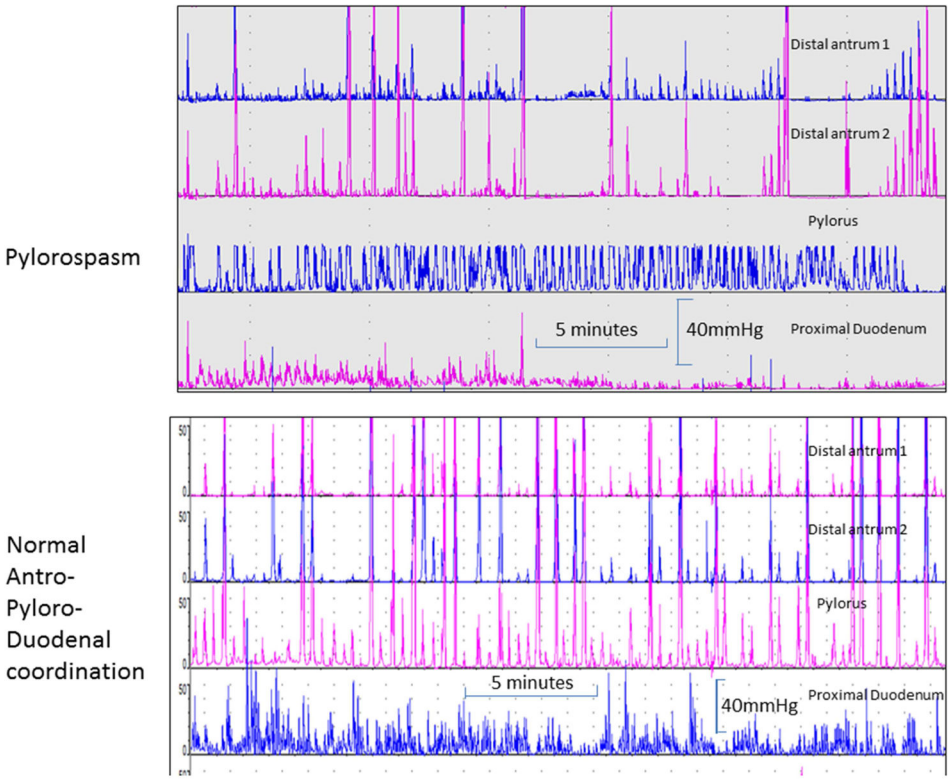

Figure 2.

Antroduodenal motility tracings in the postprandial period with sensors 1cm apart. Note in the upper example the consistent phasic and tonic contractions at the pylorus with intermittent loss of distal antral contractions 1 and 2 cm proximal to the pylorus. In contrast, note the consistent antropyloric coordination in the normal example in the lower tracings.

Table 1

Relationship between 2-hour postcibal antral motility index and gastric emptying of digestible solids or nutrient liquids relative to healthy controls in disease groups (which excluded myopathic disorders) based on manometric evaluation. Data derived from ref. 13, Camilleri et al. Gastroenterology 1986;91:94–99.

Neuropathic motility disorder	Duration of lag phase	Post-lag GE slope	GE solids	GE liquids
Antral hypomotility (AH)	Prolonged	Slower	Delayed	Delayed
Chronic intestinal dysmotility	Normal	Slower (and similar to AH)	Delayed (slightly less than AH)	Delayed (and similar to AH)

GE=gastric emptying; AH=antral hypomotility