Published in final edited form as:
Clin Gastroenterol Hepatol. 2011 January ; 9(1): 5–e7. doi:10.1016/j.cgh.2010.09.022.

Epidemiology, Mechanisms and Management of Diabetic Gastroparesis

Michael Camilleri, M.D., **Adil E. Bharucha, M.D.**, and **Gianrico Farrugia, M.D.**
Clinical Enteric Neuroscience Translational and Epidemiological Research (CENTER), Mayo Clinic, Rochester, MN

Abstract

Background—Recent evidence of the significant impact of gastroparesis on morbidity and mortality mandates optimized management of this condition. Gastroparesis affects nutritional state and, in diabetics, it also has deleterious effects on glycemic control and secondary effects on organs that lead to increased mortality. First-line treatment includes restoration of nutrition and medications (prokinetic and antiemetic).

Aim—To review the epidemiology, pathophysiology, impact, natural history, time trends and treatment of gastroparesis with particular focus on diabetic gastroparesis.

Methods—The pros and cons of current treatment options including metoclopramide are discussed. Second-line approaches include surgery, venting gastrostomy or jejunostomy, and gastric electrical stimulation; most of these treatments are based on open-label treatment trials.

Results/Conclusions—In the future, drugs that target the underlying defects and new prokinetics such as newer 5-HT_4 agonists (which appear to be devoid of cardiac or vascular effects), ghrelin agonists, new approaches to pacing the stomach, and stem cell therapies may bring more effective treatments to ameliorate the management of patients with gastroparesis.

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

Authors' roles: All authors were involved in writing the manuscript and providing critical revision of the manuscript for important intellectual content.

Disclosures of financial relationships for Dr. Camilleri:

- Research grants relevant to content of manuscript:
  - Johnson and Johnson - prucalopride
  - Theravance - velusetrag
- Honoraria below federal threshold for significant COI: Theravance, Tranzyme
- CDA with no personal remuneration: Movetis

Disclosures of financial relationships for Dr. Farrugia:

- Research grants relevant to content of manuscript: None

Disclosures of financial relationships for Dr. Bharucha:

- Research grants relevant to content of manuscript: None
- Honoraria: None

Keywords

gastroparesis; diabetes; pharmacotherapy, treatment

Introduction and Definition of Gastroparesis Syndrome

Gastroparesis is a syndrome characterized by delayed gastric emptying in absence of mechanical obstruction of stomach. The cardinal symptoms include postprandial fullness (early satiety), nausea, vomiting, and bloating. While the focus is on diabetic gastroparesis, we have included information on all gastroparesis when information specific to diabetic gastroparesis is not available in the literature. In one tertiary referral series, diabetes accounted for almost one third of cases of gastroparesis (1). Symptoms attributable to gastroparesis are reported by 5 to 12% of patients with diabetes (2,3). There is an association between self-reported glycemic control and psychological distress and development of gastrointestinal symptoms in diabetics (4). Although the majority of patients with diabetes mellitus and upper gastrointestinal symptoms have delayed gastric emptying, a subset [18.2% in one study (5)] had accelerated gastric emptying relative to healthy controls.

Epidemiology, Natural History and Impact of Gastroparesis

On January 1, 2007, the age-adjusted (to the 2000 U.S. white population) prevalence of definite gastroparesis per 100,000 persons was 24.2 [95% confidence interval (CI), 15.7–32.6] for both genders, 9.6 (95% CI, 1.8–17.4) for men, and 37.8 (95% CI, 23.3–52.4) for women (6). The corresponding incidence figures for the years 1996–2006 were 2.4 (95% CI, 1.2–3.8) for men and 9.8 (95% CI, 7.5–12.1) for women (6). These community-based epidemiological data for the first time provide data on definite gastroparesis defined as delayed gastric emptying by standard scintigraphy and symptoms of nausea and/or vomiting, postprandial fullness, early satiety, bloating, or epigastric pain for more than 3 months; these data contrast prior estimates of gastroparesis based solely on symptoms suggestive of gastroparesis without documentation of delayed gastric emptying. .

The cumulative incidence of gastroparesis is 4.8% in type I diabetes, 1% in type 2 diabetes, and 0.1% in non-diabetic people in Olmsted County, MN (7). The crude incidence rate appears to increase with age (6). This is consistent with the well-established observation (8,9) that diabetic gastroparesis typically develops after diabetes mellitus has been established for ≥10 years and patients with type 1 diabetes may have triopathy, that is, neuropathy, nephropathy and retinopathy. While gastroparesis appears to be more common in type 1 diabetes compared to type 2, the increased prevalence of type 2 diabetes has resulted in larger numbers of patients with gastroparesis associated with type 2 diabetes. In addition the use of incretin-based therapy in the latter patients is an additional risk factor for developing gastroparesis in type 2 diabetes.

Once established, diabetic gastroparesis tends to persist, despite amelioration of glycemic control. Thus, gastric emptying and symptoms are stable during ≥12 years follow-up, despite improved glycemic control (10).

Diabetic gastroparesis reduces quality of life (QOL) scores on all main domains assessed including physical, emotional, mental, social and bodily functions (11). Diabetic gastroparesis impairs mean QOL independently of other co-morbid factors such as age, tobacco, alcohol, type of diabetes mellitus (12).

In 86 patients with diabetes who were followed for at least 9 years, gastroparesis was not associated with mortality after adjustment for other disorders (13). The median time of death

was 6 years (range 1–12). The major causes of death were cardiovascular or renal disease. None of the deaths was due to trauma. Of the 62 living patients, gastric solid emptying was delayed in 32 (52%); liquid emptying in 18 (29%); and esophageal transit, in 17 (27%). In those patients who had died, the duration of diabetes (P = 0.048) and scores for autonomic neuropathy (P = 0.046), retinopathy (P = 0.017), and esophageal transit (P= 0.032) were greater than in the patients who were alive.

Although no deaths were attributed to gastroparesis in the study by Kong et al. (13), it does not mean that diabetic gastroparesis is irrelevant in the natural history of diabetes. In fact, Jung et al. (6) provided conclusive evidence that gastroparesis was associated with higher mortality and morbidity, and delayed radionuclide gastric emptying studies predict morbidity, increased hospitalizations, emergency department and doctor visits in diabetics with symptoms of gastroparesis. Patients with type 1 or 2 diabetes mellitus with classic symptoms of gastroparesis (including early satiety, postprandial fullness, bloating, abdominal swelling, nausea, vomiting, and retching) and documented delay in gastric emptying were more likely to have cardiovascular disease, hypertension and retinopathy (14), suggesting that the underlying complication may be related to micro- or macro-angiopathies, which are known complications of poor diabetic control.

The United States Medicare based data on gastroparesis-related hospitalizations in the United States from 1995 to 2004 show that hospitalizations for gastroparesis have increased since 2000 (15). In the absence of other trends in the management of gastroparesis, it is conceivable that this increase may partly be related to the introduction of an operative procedure for treatment of gastroparesis, gastric electrical stimulation (16); indeed, a meta-analysis shows device removal or reimplantation rate (which required hospitalization) was 8.3% (17), and in one series of GES treatment for diabetic gastroparesis, there were 225 gastroparesis-related hospitalizations in 40 patients (18). GES-related hospitalization is unlikely to be the sole factor for the marked increase noted since 2000. A recent study has identified, in a retrospective single tertiary referral center, the factors that contribute to hospitalization in patients with exacerbations of gastroparesis (19). The factors identified were poor glycemic control, infection, non-compliance with or intolerance of medications, and possibly adrenal insufficiency. Among these patients hospitalized with exacerbations of gastroparesis, some had elevated levels of acute phase reactants or “inflammatory markers” such as elevated erythrocyte sedimentation rate and C-reactive protein levels, in some cases in the absence of proven intercurrent infections. The cause for the elevated markers of inflammation, and the reasons for hospitalization among patients with gastroparesis require further study.

Mechanisms

Gastric emptying involves integration of fundic tone and antral phasic contractions with inhibition of pyloric and duodenal contractility. Gastric emptying requires interactions between smooth muscle, enteric and extrinsic autonomic nerves, and specialized pacemaker cells, the interstitial cells of Cajal [ICC (20)]. Several abnormalities in diabetes may result in gastric motor dysfunction (Figure 1) including autonomic neuropathy, enteric neuropathy involving excitatory and inhibitory nerves, abnormalities of ICC, acute fluctuations in blood glucose, incretin-based medications used to normalize postprandial blood glucose and psychosomatic factors (21–23).

Extrinsic nerves

Autonomic neuropathy is commonly encountered in diabetic gastroparesis. Evaluation of the vagus nerve by sham feeding shows blunted pancreatic polypeptide response (24), as well as reduced gastric secretion in patients with diabetic gastroparesis (25). Vagus nerve

dysfunction is also thought to mediate some of the acute effects of hyperglycemia as a similar effect can be induced by subdiaphragmatic vagotomy (26). Morphological studies of the vagus nerve have revealed demyelination (27).

Similarly, abnormalities have also been described in the axons and dendrites within the prevertebral sympathetic ganglia (28), suggesting that in diabetic gastroparesis both the sympathetic and parasympathetic component of the autonomic nervous system are affected. Diabetic autonomic [as well as peripheral (29)] neuropathy is at least partially reversible after restoration of normal glycemic control and renal function with pancreas-kidney transplantation, and this includes improved gastric function (30).

Enteric and intrinsic mechanisms

Experimental diabetic gastroparesis may occur due to increased levels of oxidative stress caused by low levels of heme oxygenase-1 (HO-1), an important cytoprotective molecule against oxidative injury (31). Experimental approaches that increase expression of HO-1 (32) or enhance the function of nitrergic mechanisms (33) protect against the development of gastroparesis or restore gastric emptying in diabetic mice and rats respectively.

Human and small animal studies suggest that the most common gastric cellular defects in gastroparesis are loss of expression of neuronal nitric oxide (nNOS) and loss of interstitial cells of Cajal (ICC). The loss of nNOS in enteric neurons does not appear to be due to loss of neurons that expresses nNOS because most studies using pan-neuronal markers have not observed neuronal dropout in diabetic gastroparesis. This suggests that strategies directed at restoring nNOS expression may be of therapeutic benefit. However, in non-obese diabetic (NOD) mice, the loss of nNOS occurs early after development of diabetes and is independent of the development of gastroparesis (31). Therefore, it is possible that post-translational modification of nNOS may be more important than absolute nNOS levels (34).

Loss of ICC is the most common enteric neuropathological abnormality in diabetic and idiopathic gastroparesis (35). Interstitial cells of Cajal ICC serve multiple functions in the gastrointestinal tract. ICC generate slow waves that control smooth muscle contractility, are involved in aspects of neurotransmission, set the smooth muscle membrane potential gradient and are involved in mechanotransduction (36). Recent studies have begun to unravel the complex pathways that regulate ICC networks in the gut and their dysregulation in gastroparesis. Normally, interstitial cells of Cajal networks are continuously remodeled and maintained by a balance between processes that injure and maintain ICC. In diabetic gastroparesis, this balance is shifted in favor of pathways that damage ICCs by various mechanisms including insulinopenia, IGF-1 deficiency, and oxidative stress (36). Since insulin and IGF-1 promote production of smooth muscle cell-produced stem cell factor, which is an important ICC survival factor, their deficiency in diabetes is detrimental to ICCs (37). Moreover, diabetes is a high oxidative stress state and when the mechanisms that normally counteract increased oxidative stress (e.g., upregulation of macrophage heme oxygenase-1) are impaired, ICCs are lost and gastric emptying is delayed (38). Upregulation of heme oxygenase-1 by hemin increases ICC and nNOS and normalizes delayed gastric emptying. A recent study suggests that the protective effects of heme oxygenase-1 are mediated by one of its products – carbon monoxide (39). Since hemin also increases heme oxygenase activity in humans (40), the insulin/IGF-1 and the heme oxygenase/carbon monoxide pathways provide opportunities to develop therapies that are based on the underlying pathogenesis. Also, since the gut contains interstitial cells of Cajal and enteric stem cells (41,42), targeting residual stem cells or transplantation of stem cells is a new area that deserves to be explored further.

Iatrogenic gastroparesis

Known causes of iatrogenic gastroparesis include vagal inhibition, which may be due to vagal nerve injury (e.g., after fundoplication for gastroesophageal reflux disease) or pharmacological blockade [e.g., during treatment with glucagon like peptide-1 (GLP-1) analogs for type 2 diabetes mellitus (43)]. In contrast to GLP-1 analogs, which substantially increase plasma GLP-1 concentrations, dipeptidyl peptidase IV inhibitors, which increase plasma GLP-1 concentrations to a lesser extent by inhibiting metabolism of GLP-1, do not delay gastric emptying (44). In a comprehensive review (45), nausea (43.5%) was the most commonly reported adverse event in 5 and 10 μg b.i.d. exenatide groups, and vomiting was also quite commonly encountered (12.8%). Among kidney transplant recipients, gastroparesis may be caused by treatment with cyclosporine or calcineurin inhibitors such as tacrolimus (46,47).

Pathophysiology

Delayed gastric emptying and impaired gastric accommodation

Gastroduodenal motor abnormalities in diabetic patients with delayed gastric emptying include less frequent antral contractions, antroduodenal incoordination (48,49), and pyloric spasm (50). Of note, the latter rarely occurs in isolation and is typically associated with antral hypomotility (50). Abnormalities in small bowel motility may result in delayed gastric emptying of solids (51); gastric motor dysfunction may be associated with small bowel dysmotility due to a common mechanism. In addition, disturbances of proximal gastric compliance, either (increased (52) or decreased (53), have been reported and may also contribute to symptoms.

Interstitial cells of Cajal generate an electrical signal that can be recorded using cutaneus electrogastrography (EGG). Gastric electrical dysrhythmias or reduced power of the electrical signal postprandially are found in gastroparesis; however, the precise role of electrogastrography (EGG) as currently used in screening or diagnosis of gastroparesis is still unclear (54,55). With the development of high resolution electrogastrography that can identify the origin and propagation of the electrical signaling within the stomach wall (56), it is conceivable that EGG will undergo renewed interest and application and, conceivably, usher in alternative approaches to treatment as occurred with the introduction of electrophysiology studies in the treatment of cardiac arrhythmias. However, further work is necessary to reliably differentiate signal from background noise, as well as to reliably determine slow wave frequency in a setting where several different regional frequencies may be present in different parts of the stomach.

Accelerated gastric emptying

While most attention has focused on delayed gastric emptying, rapid gastric emptying of solids and/or liquids with features of dumping syndrome and diarrhea is an increasingly recognized disorder in several conditions, i.e., after fundoplication and other gastric surgery for peptic ulcer or as a bariatric procedure, in diabetes mellitus, functional diarrhea, functional dyspepsia, and autonomic dysfunction (57–63).

At our institution, among a cohort of 129 consecutive patients with diabetes mellitus in whom gastrointestinal transit was evaluated clinically by scintigraphy, 55 (42%) had normal, 46 (36%) had delayed, and 28 (22%) patients had rapid gastric emptying of solids (61). While delayed gastric emptying has been associated with longstanding, complicated type 1 diabetes, rapid gastric emptying of liquids has been associated with type 2 diabetes, often with early disease (58,64–68). However, in the only study which incorporated patients with delayed and rapid emptying, the diabetic phenotype (e.g., type of diabetes, duration of

disease) did not predict the gastric emptying disturbance (61). A neuropathy, defined by physical examination, abnormal electromyography (EMG), or objective autonomic dysfunctions, was a risk factor for delayed gastric emptying (61).

Vagal dysfunction, as can occur in diabetes mellitus or after gastric surgery, may impair nitrergic-mediated gastric accommodation, predisposing to higher gastric pressures and rapid gastric emptying of liquids (69–72). Indeed, impaired postprandial proximal gastric accommodation (53) and exaggerated fundic phasic contractility (65) may contribute to symptoms (e.g., bloating) rapid gastric emptying in diabetes. The mechanisms of rapid gastric emptying in patients not exposed to diabetes mellitus or gastric surgery are not understood.

Patients with rapid gastric emptying present with poor postprandial glycemic control and postprandial upper abdominal symptoms (e.g., abdominal discomfort, nausea with or without vomiting), which are often indistinguishable from those of delayed gastric emptying, other than weight loss being more common among those with delayed gastric emptying (61,62).

Gastric and Enteric Neuromuscular Pathology

In the largest series of 101 patients in a referral practice with refractory and unexplained nausea and vomiting, Abell et al. (73) reported a high incidence of small bowel morphologic abnormalities (primarily neuropathies).

Other reports with smaller numbers of patients have documented that histologic abnormalities are heterogeneous and include myenteric inflammation, decreased innervation, reduction of ICCs (74), muscle fibrosis (75), or smooth muscle degeneration and fibrosis with eosinophilic inclusion bodies (76). Absence of ICCs was associated with abnormal gastric slow waves, worse symptoms of gastroparesis, and less improvement with gastric electrical stimulation (77).

Novel, less invasive methods to obtain full-thickness gastric biopsies endoscopically or percutaneously have been described in pigs and dogs (78–80). Pathological examination may confirm the organic nature of gastric stasis, and may provide information, such as neuropathic or ICC disorders may be more responsive to treatment than myopathies.

Gastric Emptying and Symptoms in Gastroparesis

The relationship between abnormal gastric emptying and abdominal symptoms is an area of considerable discussion. Gastric retention may be asymptomatic (8), possibly due to the afferent dysfunction associated with vagal denervation (81). Moreover, in addition to delayed gastric emptying, other mechanisms (e.g., impaired gastric accommodation, visceral hypersensitivity) also contribute to upper gastrointestinal symptoms (82). Thus, the reported poor correlation between global symptoms and gastric emptying (83), and the non-significant impact of tegaserod on upper gastrointestinal symptoms in functional dyspepsia is not surprising (84). However, these findings should not imply that delayed gastric emptying is not relevant to symptom generation or that it is not useful to document delayed gastric emptying in patients with upper gastrointestinal symptoms. To the contrary, fullness, upper abdominal pain and reduced hunger correlate better with delayed gastric emptying than nausea and vomiting (82,85), and, when prokinetic therapy is limited to patients who have delayed gastric emptying at baseline, therapy significantly improves upper gastrointestinal symptoms (86,87). Since accelerated gastric emptying can present with similar symptoms, it is useful to measure gastric emptying, fundic relaxation and antral contractility (5,82) before selecting therapy.

Abdominal pain is an often under-appreciated symptom in gastroparesis. In a multicenter study from an NIH consortium on gastroparesis, 72% of patients with gastroparesis had abdominal pain, which was the dominant symptom in 18% (88), reflecting the heterogeneous patient population in this cohort. A tertiary referral study showed that abdominal pain was reported in 90% of 68 patients with delayed gastric emptying (18 diabetic and 50 idiopathic gastroparesis). Pain was induced by eating (72%), was nocturnal (74%), and interfered with sleep (66%). Severity ranking of abdominal pain was in the same range as other symptoms (e.g., fullness, bloating, nausea) and was not correlated with gastric emptying rate, but was associated with impaired quality of life. The preponderance of the idiopathic group and large proportion of daily (43%) or even constant pain (38%) in this cohort of patients suggest tertiary referral bias (89). Psychological dysfunction is associated with symptom severity (2,90).

Diagnosis of Gastroparesis

Gastroparesis is diagnosed by demonstrating delayed gastric emptying in a symptomatic patient after exclusion of other potential etiologies of symptoms and obstruction with endoscopy or radiological imaging. When the delay is asymptomatic, the term delayed gastric emptying instead of gastroparesis should be used. The current diagnostic method of choice is scintigraphic measurement of the emptying of solids (91). In the absence of obstruction, retained food in the stomach after an overnight fast demonstrated at endoscopy is suggestive of ineffective antral interdigestive motility and gastroparesis. Absence of the antral component of the migrating motor complex is associated with postprandial antral hypomotility (92). Some patients with retained food at endoscopy may have normal scintigraphic emptying, suggesting relatively preserved postprandial antral motility to triturate and empty a digestible meal (during scintigraphy), but abnormal interdigestive antral motility which impairs emptying from the stomach between meals of particles larger than 2 mm in size.

Management of Diabetic Gastroparesis

The principles in management of diabetic gastroparesis (93) are summarized in Table 1.

Current Prokinetics

The evidence for use of current prokinetics is based on trials performed two or three decades ago. Therefore, the level of evidence might not pass muster relative to the rigorous, large trials with validated patient response outcomes required nowadays. These include validated instruments that track patient symptoms on a daily basis, such as the daily diary Gastroparesis Cardinal Symptom Index (94), and a validated instrument to assess quality of life specific for upper gastrointestinal disorders, the Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life [PAGI-QOL (95)].

The next section summarizes some of the clinical trials that provide the basis for current prokinetic therapy.

a. In a 3-week, double-blind, multicenter, placebo-controlled trial, ***metoclopramide***, 10-mg tablet qid, was tested in 40 patients with diabetic gastroparesis (96). There was evidence of reduced nausea, vomiting, fullness, early satiety and improved meal tolerance, of significantly reduced nausea and post-meal fullness, and of significantly improved gastric emptying relative to baseline (though no significance between the metoclopramide and placebo treatment arms). Metoclopramide is a 5-HT_4 receptor agonist and a dopamine receptor antagonist; the latter, partly centrally-mediated effect may explain improvement in nausea.

b. In a double-blind, multicenter comparison of 4 weeks' treatment of diabetic patients with symptoms of gastroparesis, ***domperidone*** (a more selective dopamine antagonist with lesser central penetration) and metoclopramide were equally effective in alleviating symptoms of diabetic gastroparesis. Adverse central nervous system effects were more severe and more common with metoclopramide treatment, including somnolence and reduced mental acuity (97). Domperidone is available for use under a special program administered by the Food and Drug Administration.

c. ***Erythromycin***'s prokinetic effects in gastroparesis involve two different pathways, activating motilin receptors on cholinergic receptors on neurons and smooth muscle (98). Erythromycin lactobionate is most effective when given intravenously at a dose of 3mg/kg every 8 hours (by intravenous infusion over 45 minutes to avoid sclerosing veins), as was shown in hospitalized diabetics with gastroparesis (99). There is evidence that many motilin agonists, including erythromycin, are associated with tachyphylaxis due to down regulation of the motilin receptor. This was also observed in an open trial of idiopathic and diabetic gastroparesis with acute intravenous and chronic oral erythromycin. Clinical responsiveness drops after 4 weeks (100); however, some patients continue to experience benefit. A short-term clinical trial using erythromycin or newer drugs such as azithromycin is worthwhile. This especially is the case if the patient does not tolerate metoclopramide or requires a “drug holiday” from metoclopramide, or if domperidone is unavailable, or if these prokinetics are not controlling the patients' symptoms.

Symptomatic Treatment of Nausea, Vomiting and Pain in Gastroparesis Syndrome

The etiology of abdominal pain in gastroparesis is not well understood. Other than prokinetics, the symptomatic treatment of these symptoms therefore remains empirical and off-label use of these drugs from the indications for non-specific nausea and vomiting, or chemotherapy-induced emesis and palliative care. The most commonly prescribed antiemetic drugs are the phenothiazines (including prochlorperazine and thiethylperazine) or antihistamine agents (including promethazine, or meclizine). There are no studies that compare efficacy of phenothiazines with newer anti-emetics (such as serotonin 5-HT_3-receptor antagonists) for gastroparesis; clinical practice suggests comparable efficacy for most patients. Given lower costs, it is reasonable to start with antihistamines and phenothiazines before escalating to more expensive drugs. 5-HT_3-receptor antagonists are a reasonable second line medications; the neurokinin receptor-1 antagonist, aprepitant, is effective in treatment of delayed chemotherapy-induced nausea and vomiting (101). Studies of effectiveness of these classes of drugs in the nausea and vomiting of gastroparesis are not yet available. The synthetic cannabinoid, dronabinol, is also used in practice, but there is risk of hyperemesis on withdrawal (102), and optimum treatment strategies are unclear. Transdermal scopolamine, which is effective for nausea associated with motion sickness, is used for nausea and vomiting of gastroparesis, albeit without peer-reviewed publications to support this practice. Among alternative medicine therapies, acupuncture is the method most studied in treatment of nausea and vomiting; one study reported impressive relief in 94% of patients (103).

The management of pain remains a challenge, which has not been addressed in clinical trials of patients with gastroparesis. Tricyclic antidepressants, which are somewhat effective for abdominal pain in functional bowel disorders, are often used as first line therapy for pain in gastroparesis. Second line approaches for the pain in gastroparesis are the weak μ-opioid

receptor agonist, tramadol (which also releases serotonin and inhibits the reuptake of norepinephrine), and the gamma-aminobutyric acid analog, gabapentin.

Should Metoclopramide Be Used in Patients with Gastroparesis?

An FDA black box warning informed practitioners about the adverse effects of metoclopramide, especially tardive dyskinesia, an irreversible neurological complication that may affect orofacial, lingual and axial muscles and may interfere with nutrition, manual dexterity and ambulation. Development of this condition is directly related to the duration of metoclopramide use and the number of doses taken. Older patients, especially women, are at greatest risk. The FDA recommended that treatment with metoclopramide should not exceed three months. Neurologic side effects of metoclopramide include the extrapyramidal symptoms of pseudo-parkinsonism, akathisia and acute dystonic reactions. These side effects often respond to reduction in dosage or cessation of the medication, and to anticholinergic medications such as benztropine. When metoclopramide is stopped, a withdrawal dyskinesia can develop which typically resolves. However, the more serious adverse effect is tardive dyskinesia or tardive dystonia which may appear during or after stopping metoclopramide, and which does not resolve with reducing the dosage or discontinuing therapy. There is, therefore, a risk of potentially permanent neurological sequelae with metoclopramide treatment. The controversial issue is: what is the real prevalence of such permanent tardive dyskinesia or dystonia?

We believe that national prescription data bases provide more valid estimates of the true prevalence and, therefore, the the risk of metoclopramide-associated tardive dyskinesia than case series from tertiary referral movement clinics. The national prescription data bases suggest the risk of metoclopramide-induced tardive dyskinesia is likely far less than 1% (104), which is much lower than the estimated 1–10% risk previously suggested in national guidelines (105,106). Since the incidence is so low, tardive dyskinesia may represent an idiosyncratic response, conceivably related to genetic susceptibility (104), as with neuroleptic agents and the tardive dyskinesia which have been linked to genetic variation in dopamine receptors (107,108).

The evidence in favor of use of metoclopramide is weak; the availability of alternative, approved medications would easily displace it from the prescription pads of physicians, as occurred when cisapride was generally available for prescription. It is essential that any physician prescribing metoclopramide obtains and documents informed consent. The American Psychiatric Association addressed the issue of late neurological effects of antipsychotic drugs and made the following recommendations: First, while the problem is serious, an alarmist view is unwarranted, especially since many cases are detected early and improve spontaneously. Second, the use of antipsychotic drugs should be reserved for clear indications and, third, the APA recommended a search for new agents with much less adverse neurologic effect but with adequate antipsychotic efficacy (109).

Rao and Camilleri (104) proposed the following principles for use of metoclopramide: First, metoclopramide should be reserved for patients with documented gastroparesis (by symptoms and gastric emptying scintigraphy). Second, since tardive dyskinesia may be reversible with discontinuation of metoclopramide, it should first be prescribed for a trial period, and the lowest effective dose for the individual patient should be sought. Third, the liquid formulation may produce more predictable plasma drug levels and permit easier dose titration. An alternative approach is to use orally dissolvable formulation (110).

In summary, a judicious start with a test dose (e.g., 5mg, 15 minutes before meals and at bedtime), titrating to the lowest efficacious dose, and giving the patient `drug holidays' or

dose reductions (e.g., 5mg, before two main meals of the day) whenever clinically possible (104) should guide the use of metoclopramide.

The medication, domperidone, appears to be equally efficacious and safer than metoclopramide (97) and would be a safer alternative if it was approved for prescription in the United States (111).

New Prokinetic Agents

a. Azithromycin

Intravenous azithromycin was compared to erythromycin in a study of antral motility (phasic pressure activity) in patients with chronic functional gastrointestinal pain and gastroparesis (112). The mean amplitude, duration of high amplitude contractions, and motility index were higher with azithromycin. Further validation studies and symptom assessments are needed in patients with gastroparesis.

b. TZP-101

In a controlled, crossover, scintigraphic gastric emptying study (113), the ghrelin analog TZP-101 (80, 160, 320 or 600 μg/kg) administered intravenously was tested in 7 type 1 and 3 type 2 diabetics with moderate to severe gastroparesis symptoms and >29% retention of a solid egg radiolabeled meal at 4 hours after ingestion. TZP-101 reduced the $t_{1/2}$ for gastric emptying of solids (i.e., mean acceleration of 20%) and shortened the lag time (mean reduction 34%) relative to placebo. TZP-101 also reduced overall post-meal symptom intensity (24%) and postprandial fullness (37%). The study did not have sufficient power to assess significance of change of symptom endpoints. Most adverse events were mild and self-limiting.

A more recent analysis (114) compared the effects of TZP-101, at varying daily doses from 20–600 μg/kg intravenously (n=17), and placebo (n=6) in patients with severe gastroparesis (nausea and vomiting GCSI score >3.5). In a post-hoc analysis of 6 patients who received 80 μg/kg TZP-101 compared to 6 who received placebo, TZP-101 improved symptoms (nausea/vomiting subscale and total GCSI score) after treatment for 4 days; this improvement was sustained at the 30 day follow-up period (114). However, the higher doses, which also accelerated gastric emptying at pharmacological doses (114,115), were not as effective as the 80 μg/kg for improving symptoms. One potential explanation of this apparent paradox is that ghrelin agonists reduce gastric accommodation and induce certain upper gastrointestinal symptoms (116).

c. Motilides

Several motilides, which are devoid of some undesirable features of erythromycin (e.g., tachyphylaxis, antibiotic action, effects at hERG channels) are being assessed for gastroparesis. GSK962040 is a recently identified small molecule, non-motilide motilin receptor agonist (117) which selectively activates the motilin receptor in humans and is being evaluated to determine safety and tolerability in humans (118). Another motilin agonist in development is RQ-00201894 (119). As with ghrelin agonists, motilin agonists may increase gastric tone or inhibit gastric accommodation and, potentially, induce worse symptoms, even when gastric emptying improves.

New-Generation 5-HT_4 Agonists

New-generation 5-HT_4 agonists have high selectivity for 5-HT_4 receptors, with little affinity for other serotonergic and other classes of receptors; in addition, they affect the arrhythmia-mediating delayed rectifier potassium current at concentrations >300-fold greater than

cisapride, suggesting a considerable margin of cardiac safety. Three of these agents are *prucalopride* which accelerated gastric emptying in patients with functional constipation (120), *velusetrag* (121) and *ATI-7505* (122) which accelerated gastric emptying in healthy subjects.

Intra-pyloric Botulinum Toxin Injection

Despite several open trials suggesting efficacy, two randomized, controlled trials showed the same disappointing results: no efficacy on symptom or objective endpoints of gastric emptying (123,124). Based on these studies there is no role for intra-pyloric botulinum toxin injection in the treatment of gastroparesis, despite its extensive use in practice.

Gastric Electrical Stimulation

Gastric electrical stimulation (GES) refers to the delivery of high frequency (several fold higher than the intrinsic frequency) lower energy electrical stimulation to the stomach. The device was approved by the FDA as a humanitarian device exemption (16). The device was approved based on a double-blind study that reported improvement of weekly vomiting frequency and quality of life in 33 patients with diabetic and idiopathic gastroparetics and has been available for a decade. There was overall efficacy in the whole patient cohort studied; however, there was no evidence of benefit in idiopathic gastroparesis. In addition, it is important to note that the study was reported when only about 70% of the planned study population had competed studies. With one exception, subsequent reports have been open label studies and reports generally support some improvement in symptoms, reduced need for nutritional support and increased quality of life for children, diabetics and post-surgical gastroparetics. A meta-analysis (17) suggested that, among 13 included studies, 12 lacked controls and only 1 was blinded and randomized. Results showed substantial benefits for high frequency gastric electrical stimulation for the treatment of gastroparesis. However, caution is necessary in interpreting the results, primarily because of the limitations of uncontrolled studies and, therefore, further controlled studies are required to confirm the clinical benefits of high frequency gastric electrical stimulation.

Preliminary reports (18) of a multicenter, randomized, controlled study conducted and involving 55 patients with diabetic gastroparesis (mean age 38, 66% female, average 5.9 years of gastroparesis) showed no significant difference in weekly vomiting frequency (WVF) between on versus off periods during cross-over (median $\Delta = 0\%$, $p=0.215$). However, at 1 year post-implant, when all patients had the device on, the WVF remained lower than baseline (median reduction of WVF of 67.8%, $p<0.001$). This was accompanied by a significant improvement in other symptoms of gastroparesis and faster gastric emptying (median retention at 4 hours of 20.5% versus 46.5% at baseline [$p<0.001$ (125)].

One interpretation of the trial is that the initial on period prior to randomization may have rendered the cross-over results null; however, the crossover trial results are unequivocal, and the results after 1 year reflect the previously reported open-label experience. Similar reports have been recorded in idiopathic gastroparesis (114).

The mechanism of symptom relief with gastric electrical stimulation is still unclear. Some authors (126,127) have proposed that gastric electrical stimulation results in changes in the central mechanisms that control nausea and vomiting, that GES increases vagal function, also resulting in increased fundic accommodation and perhaps decreased sensitivity to distension. In a very small number of patients thalamic and caudate nucleus activity was shown to be increased on PET imaging during gastric electrical stimulation (126). While these hypotheses may fit some of the observations, it is important to note that there is still no

evidence that vomiting center function is actually altered, and the relationship between the described changes and the WVF requires more study.

Most patients who respond to GES do so relatively soon after implantation of the device. This has led to the proposal that temporary endoscopic placement of stimulation leads in the stomach can be used to predict response to the permanent device (see below).

New Paradigms of Gastric Electrical Stimulation

The choice of the current parameters used in GES where partly based on battery considerations. New approaches (128–130) are being proposed to high frequency gastric electrical stimulation (Table 2). Assessment of the efficacy of these new paradigms may be facilitated in the future with a recently described method (131) to assess entrainment mapping with large numbers of sensors including three printed circuit boards over an area of 47cm^2.

Venting Gastrostomy or Jejunostomy

In patients with significant upper gastrointestinal motility disorders, surgically-placed venting gastrostomy, with or without a venting enterostomy, reduced hospitalization rate by a factor of 5 during the year after placement (132,133). Results of endoscopic venting (PEG, direct PEJ) on nutritional outcomes and gastroparesis symptoms have not been formally studied and, therefore, remain unclear. However, an open-label experience suggests that weight can be maintained and total symptom score reduced up to three years post-venting gastrostomy (134).

Gastrectomy

While completion or subtotal gastrectomy was applied most often for gastroparesis that followed gastric surgery for peptic ulcer disease (135,136), experience from tertiary referral centers suggests that in carefully selected patients, major gastric surgery can effectively relieve distressing vomiting from severe gastroparesis and improve quality of life (76,137) in seriously affected patients where risk of subsequent renal failure is high and where life expectancy is poor. The risk of malnutrition and weight loss following gastrectomy has to be weighed relative to the symptom relief.

Stem Cells

Given the loss of key factors that control gastric motility such as loss of nNOS in enteric neurons and loss of ICC, cellular transplantation has been proposed as a therapy for gastroparesis (138). Transplanted neuronal stem cells were shown to survive in the pyloric wall of nNOS$^{-/-}$ mice as neurons and glia. The grafted neuronal stem cells expressed nNOS, but not VIP; on the other hand, VIP immunoreactivity was found in intrinsic ganglia. The transplantation of the neuronal stem cells surviving in the nNOS$^{-/-}$ mice is associated with improved liquid gastric emptying (138). ICC stem cells have also been identified, suggesting a similar approach may be possible to replenish the population of ICC or strategies employed to target residual stem cells (139).

While these observations are promising, the potential of inducible pluripotent stem (iPS) cells derived from somatic cells represents a novel renewable source of tissue precursors. The potential of iPS cells is considered to be equivalent to that of human embryonic stem cells, facilitating the treatment or cure of diabetes mellitus and its neurodegenerative complications with the potential of evading the adaptive immune response that otherwise limits allogeneic cell-based therapies. It remains to be determined if the intricate extrinsic

and enteric neural apparatus and the intrinsic cells of Cajal can be reconstituted to restore normal gastric function and reverse gastroparesis.

Diabetic Gastropathy with Accelerated Emptying

The principles of management of rapid gastric emptying are avoidance of consuming fluids during and 30 minutes after meals; addition of dietary fiber supplements (e.g., pectin, guar gum, and locust bean gum) to delay gastric emptying and also improve glycemic control by reducing intestinal glucose absorption (140–144); in diabetics, treatment with the GLP-1 agonist exenatide (145) and in non-diabetics, with short- or long-acting octreotide may be required in addition to the dietary maneuvers (146–148).

Summary and Look to the Future

While a cure for diabetic gastroparesis is desirable and appears potentially feasible offering hope for the future, there are many patients that still need care now. The only community-based data (6) of definite gastroparesis (that includes evidence of gastric emptying delay) suggest that diabetic gastroparesis fulfills criteria as an orphan disease, as it affects fewer than 200,000 people nationwide (149). Assuming a U.S. population of 309.3 million people (150), the estimated U.S. prevalence of definite gastroparesis is less than 100,000. These unique, community-based data suggest that regulatory authorities should examine whether diabetic gastroparesis qualifies for orphan disease status.

Given these data and the paucity of medications available for treatment of patients with gastroparesis, there is an urgent need for Federal Drug Administration guidance to stimulate the development of “orphan drugs” for gastroparesis, consistent with the expectation that developing an orphan drug may generate relatively small sales in comparison to the cost of developing the drug, but development of the drug is in the public interest. A good, safe prokinetic is essential for patients with gastroparesis, especially since the FDA issued a warning about the use of metoclopramide. Emerging medications have promise, including ghrelin agonists and new generation 5-HT_4 agonists. High frequency gastric electrical stimulation is currently used in patients with severe symptoms based on its approval for humanitarian use, but the evidence of its efficacy is based mostly on open-label experience. In addition, the optimal conditions for entraining the electrical pacesetters that control gastric motor function are still being developed, and it is possible that advances in electrical stimulation may ultimately achieve the clinical promise that has been a goal for at least three decades. Better methods to detect the underlying electrical signal including mucosal EGG may clarify the role of EGG as well as predict response to gastric electrical stimulation.

We also need to determine if the same therapies work equally in idiopathic gastroparesis and in gastroparesis due to type 1 and type 2 diabetes or if we need to treat them differently.

Meanwhile, the management of patients requires coordinated, often multidisciplinary care that restores nutrition, hydration, electrolyte homeostasis, and controls symptoms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Support: The authors are supported by PO1 DK68055-04 from National Institutes of Health.

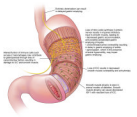

Figure 1.
Pathophysiology of diabetic gastroparesis (adapted from article in press by Farrugia G)

Table 1

Principles in the Management of Diabetic Gastroparesis

- Restore hydration, electrolytes, nutrition (enteral is preferable to parenteral) and glycemic control
- Antiemetic with caution (due to interactions in drugs involved in CYP 450 metabolism)
- Current prokinetics: 5-HT_4 agonists, dopamine antagonists
- Pain relief without narcotics: tramadol 50–75mg
- Surgery and venting gastrostomy; Botox injections
- Gastric electrical stimulation

Table 2

New Paradigms of Gastric Electrical Stimulation

Gastric Electrical Stimulation	Frequency	Pulse Width	Other Comments
Long pulse, high energy	3/min	Single pulses, 10 to 600ms	Aims to pace stomach
Single channel, 2 electrodes		Long pulses	Tested in humans and animals with gastroparesis
2–4 channels	1.1 x intrinsic frequency	Long pulses, 10–300ms, 0.5–3mA	6-week study shows reduced tachygastria and symptom scores, improved gastric emptying
Temporary trans-endoscopy or -PEG	frequency, 14 Hz	pulse width, 330 ms	Other parameters of stimulation: amplitude, 5 to 10 mA; cycle ON, 0.1 to 1.0 seconds; cycle OFF, 5.0 to 4.0 seconds. Improved symptoms and gastric emptying, especially in young age and high baseline vomiting score