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Treatment Challenges in the Management of Gastroparesis-Related GERD

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Abstract

The relationship between gastroparesis and GERD is multi-factorial. The delay in gastric emptying associated with gastroparesis can lead to prolonged gastric retention of food that may have a propensity to reflux. Because gastroparesis allows material to remain in the stomach, there is an increase in the gastroesophageal pressure gradient, gastric volume, and the volume of potential refluxate. Additionally, the prolonged exposure of material in the stomach can increase gastric acid secretion. The onset of gastroparesis has been attributed to several causes, including comorbidities (mainly diabetes), surgical complications, and the use of specific medications (including anticholinergics, narcotics, tricyclic antidepressants, and calcium channel blockers). The etiology of some cases of gastroparesis remain unclear, a condition termed idiopathic gastroparesis. Symptoms commonly associated with gastroparesis or GERD, including nausea, vomiting, and regurgitation, may delay drug absorption. This has the potential to greatly impact systemic absorption and concentration of drugs. Several patient populations may benefit from the use of medication formulations that offer an alternative to swallowing a traditional tablet. In addition, prokinetic drugs, such as metoclopramide, are used in the first-line treatment of gastroparesis to improve the contractility of the gut muscles, as well as the movement of contents through the gastrointestinal system and regulate drug metabolism and absorption.

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Target Audience: This activity has been designed to meet the educational needs of gastroenterologists involved in the management of patients with gastroparesis and/or GERD.

Statement of Need/Program Overview: Chronic gastroparesis and gastroparesis-related reflux result from a variety of causes including functional disease, chemotherapeutic treatment, and as a comorbidity of long-term diabetes. Reflux and GERD symptoms may stem from chronic gastroparesis. In these cases, patients may not respond to conventional medical therapies such as proton pump inhibitors, which aim to suppress gastric acid rather than addressing the anatomic functional dysregulations that cause gastroparesis and emesis. Unfortunately, the very nature of these conditions make the oral administration of any medication a challenge, both in terms of systemic absorption and patient disinclination to swallow pills. The development of a fast-dissolving tablet formulation of a prokinetic or antiemetic agent, which requires no intake of water and no swallowing, may provide a viable alternative for patients whose swallowing capacity is severely compromised, as well as those who are bed-ridden or lacking in ability to absorb medications via the gastrointestinal tract.

Educational Objectives: After completing this activity, the participant should be better able to:

1. Describe the pathophysiologic relationship between gastroparesis and GERD symptoms.
2. Summarize the medical and surgical options for direct treatment of gastroparesis to relieve symptoms of reflux, nausea, and vomiting.
3. Describe the special needs of patients with gastroparesis and functional swallowing disorders and the best ways to address them when administering therapy.

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Pathophysiologic Relationship Between Gastroparesis and GERD

Henry P. Parkman, MD

The gastrointestinal motility disorder gastroparesis is characterized by delayed gastric emptying in the absence of a mechanical obstruction.[1] Although symptoms of gastroparesis may vary from patient to patient, they generally include nausea, vomiting, early satiation, bloating, and upper abdominal discomfort, along with objective evidence of gastric retention.

Gastroparesis is an increasingly recognized disorder. An examination of a representative sample of US hospitalizations showed that those with gastroparesis as the primary diagnosis increased by 158% between 1995 and 2004 (from 3,977 to 10,252 hospitalizations).[2] The incidence of hospitalizations with gastroparesis as the secondary diagnosis increased by 136% during the same period (from 56,726 to 134,146 hospitalizations). Although the cause of this marked increase is unclear, possible explanations include an increase in the prevalence of gastroparesis, changes in the diagnostic criteria and treatment of gastroparesis, or improved recognition and diagnosis of the disorder.

Interestingly, gastroparesis disproportionately affects females. A study of 146 gastroparesis patients reported 82% as female.[3] In 2009, a study from the Olmstead County, Minnesota medical database reported the age-adjusted prevalence of gastroparesis between 1996 and 2006 was nearly 4-fold higher for women compared with men (37.8 versus 9.6 cases per 100,000 persons).[4] Although the reason for this increased prevalence in women is unknown, it is noted that women often experience slower gastric emptying rates when compared with men, particularly during the luteal phase of their menstrual cycle.[5,6] Several studies have investigated a potential relationship between gastroparesis and the female hormones estrogen and progesterone, although this association remains unproven.[7,8]

Diagnosis of Gastroparesis

The diagnosis of gastroparesis is accomplished with the observation of delayed gastric emptying and associated symptoms after exclusion of other causes, including mechanical obstruction. Mechanical obstruction is often excluded via upper endoscopy, although a radiographic upper gastrointestinal series is also appropriate. A gastric emptying scintigraphy test of a solid-phase meal is the gold standard for the diagnosis of gastroparesis.[1] Measurement of gastric emptying of solids is preferred over liquids, because gastric emptying of liquids may appear normal even in patients with advanced gastroparesis. Typically, a low-fat egg white meal cooked with a radioisotope is consumed with postprandial imaging conducted at 0, 1, 2, and 4 hours.[9] Recently, this method was advocated as a standard diagnostic approach by a joint consensus from the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine.[10] A newer diagnostic technique to measure gastric emptying measures the motility of a nondigestible wireless capsule. The capsule is capable of measuring several variables at regular intervals, including pH, pressure, and temperature; an abrupt change from acid to alkaline pH associated with a burst of phasic contractions is indicative of movement of the capsule from the stomach into the duodenum. A study of the diagnostic efficacy of this capsule compared with a traditional gastric emptying scintigraphy test found that the data from the capsule effectively distinguished healthy subjects from patients with gastroparesis, with a sensitivity and specificity similar to a 4-hour gastric emptying scintigraphy test.[11] Breath testing using the nonradioactive isotope 13C bound to a digestible solid may become a common method for the diagnosis of gastroparesis. Once ingested and emptied from the stomach, the 13C-containing material is metabolized to $13CO_2$, which is then expelled from the lungs during respiration.[1] These 13C breath tests provide reproducible results that correlate well with gastric emptying scintigraphy test results.[12-14] Although breath testing is currently reserved for clinical research studies, its potential applicability at the hospital bedside and in the community, where facilities for scintigraphy testing may not be readily available, makes it an attractive alternative diagnostic method for the future.

Pathophysiology of Gastroparesis

The majority of cases of gastroparesis are due to three etiologies—diabetes, postsurgical, and idiopathic. Gastroparesis is a classic complication of diabetes mellitus

Table 1. Diabetic Gastroparesis

- Diabetes is the second leading cause of gastroparesis
- Approximately 5.4 million people with diabetes have gastroparesis
  - 27% to 58% of people with type 1 diabetes exhibit delayed gastric emptying
  - 30% of people with type 2 diabetes exhibit delayed gastric emptying
- People with diabetes tend to present with a long list of comorbidities
  - Possible pill burden
  - Possible compliance issues
- Gastroparesis in people with diabetes may lead to
  - Poor glucose control
  - Complications of diabetes
- Diabetes is a rapidly growing health concern[1]
  - From 1980 to 2005, the incidence of diagnosed diabetes increased by 120%
  - Type 2 diabetes accounts for 90% to 95% of all diagnosed cases in adults
- Population with pre-diabetes is also on the rise
  - In 2007, at least 57 million Americans were found to have pre-diabetes
- Up to 70% of people with diabetes have mild to severe forms of nervous system damage
  - Slowed digestion of food in the stomach is a common result of such damage

Chey W. The global GERD epidemic: definitions, demographics, and the clinical implications of changing population trends. CME presentation. http://www.medscape.com/viewarticle/560076; WHO (World Health Organization) 2007; Hasler. Medscape J Med. 2008;10:16; National Institutes of Health, US Department of Health and Human Services. National Diabetes Statistics, 2007. Bethesda, MD: National Institutes of Health; 2008. NIH publication 08-3892; National Diabetes Fact Sheet, 2007. Centers for Disease Control. http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2007.pdf.

(Table 1).[15] Although it is primarily associated with type 1 diabetes, occurring in 25–55% of patients, it has also been described in 30% of patients with type 2 diabetes.[1,16-18] With the rising prevalence of type 2 diabetes, gastroparesis as a complication of this form of diabetes is also increasing. Postsurgical gastroparesis may result as a complication of several different types of surgical procedures. These surgical procedures can include vagotomy with gastric drainage for refractory peptic ulcer disease, fundoplication for treatment of gastroesophageal reflux disease (GERD), bariatric surgery for morbid obesity, and heart and lung transplantation surgery.[19-22] Generally, postsurgical gastroparesis arises in cases in which damage to the vagus nerve occurred during the procedure. Finally, idiopathic gastroparesis is diagnosed in patients who have no primary underlying abnormality. Idiopathic gastroparesis accounts for over one-third of gastroparesis cases encountered.[3]

Several intrinsic mechanisms have been attributed to the pathogenesis of gastroparesis. Neuronal nitric oxide and the enzyme responsible for its synthesis, neuronal nitric oxide synthesis (nNOS), have emerged as key molecules important in the pathogenesis of gastroparesis. NOS1-/- knockout mice, which do not express the gene encoding for nNOS, have grossly enlarged stomachs; further, pharmacologic inhibition of nNOS can delay gastric emptying in otherwise healthy animals.[23-26] Multiple animal studies, primarily in rodents, have shown that diabetes is associated with changes in both the expression and activity of gastric nNOS.[27-29] Although unknown, possible mechanisms for diabetes-induced changes in nNOS include neuronal loss or degeneration, inhibition of nNOS transcription due to reduced insulin levels, or changes in post-translational modification of nNOS.[30] One study showed that the release of the neurotransmitter acetylcholine from vagal nerve endings regulates the expression of nNOS in enteric motor neurons.[31] Depletion of the interstitial cells of Cajal (ICC) is also a noted effect in rodents with diabetes.[32] These cells, which act as pacemakers for the stomach, may require nNOS for maintenance, as well as insulin.[33,34]

Disorders of the extrinsic nervous system have also been explored as mechanisms for the pathogenesis of gastroparesis. Chronic diabetes may result in physical changes to both the motor and sensory components of the vagus nerve.[35,36] Because autonomic neuropathy is a frequent complication of diabetes, this mechanism may at least in part explain diabetes-induced changes in nNOS.

Gastroparesis and GERD

The relationship between gastroparesis and GERD is multifactorial. The delay in gastric emptying associated with gastroparesis can lead to prolonged gastric retention of food that may have a propensity to reflux, thus resulting in GERD.[37,38] Because gastroparesis allows material to remain in the stomach, there is an increase in the gastroesophageal pressure gradient, gastric volume, and the volume of potential refluxate. Additionally, the prolonged exposure of material in the stomach can increase gastric acid secretion. Another important association between GERD and gastroparesis may stem from the development of gastric distension caused by gastric emptying. This gastric distention may provoke the transient lower esophageal sphincter relaxations that are intimately involved in determining gastroesophageal reflux. In a patient with GERD symptoms of heartburn, other gastrointestinal symptoms such as early satiety, nausea, and vomiting suggest that the patient may also have gastroparesis. The presence of delayed gastric emptying may be a reason for a suboptimal treatment response in these patients.

A study of the incidence of gastroparesis in 100 patients with gastroesophageal reflux showed 41% had delayed gastric emptying.[39] The incidence of delayed gastric emptying in patients with GERD was confirmed in other recent studies as well.[40] It is generally accepted that delayed gastric emptying occurs in 10–33% of adult patients with GERD.[41] However, certain patient populations, such as diabetic patients, may be at an increased risk for both conditions.[42-45]

Conclusion

It is important to recognize that gastroparesis may be a complication in a patient with GERD, as this can greatly impact their therapy. Studies have demonstrated a rising incidence of gastroparesis in the community and an association with other chronic disease states with an expanding prevalence, particularly type 2 diabetes. Prolonged gastric retention of food and gastric distention caused by delayed gastric emptying can increase acid levels as well as affecting lower esophageal sphincter function, potentially causing GERD or exacerbating existing GERD symptoms. Gastroparesis may also substantially impact drug administration and absorption, and thus the administration of oral drugs to patients with GERD may be challenging if underlying gastroparesis is not addressed.

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Challenges Associated with the Treatment of Patients with Gastroparesis and GERD

Ronnie Fass, MD

The etiology of gastroparesis varies among patients.[1] The onset of gastroparesis has been attributed to several causes, including comorbidities (mainly diabetes, although metabolic and neurologic disorders have also been implicated), surgical complications, and the use of specific medications (including anticholinergics, narcotics, tricyclic antidepressants, and calcium channel blockers).[2] Additionally, the etiology of some cases of gastroparesis remain unclear, a condition termed idiopathic gastroparesis. The severity of gastroparesis may also vary from patient to patient, and, not uncommonly, progress over time. Diabetic patients with poor glycemic control may demonstrate an exacerbation of gastroparesis-related symptoms over time and in correspondence with abnormal glycemic levels.[3] The potential relationship of gastroparesis symptoms to gastroesophageal reflux disease (GERD) can further complicate treatment, particularly when the severity of gastroparesis fluctuates, as in some patients with underlying diabetes mellitus. Gastroparesis has been shown to exacerbate GERD symptoms, through the retention of stomach-distending foods, and hindering GERD treatment by preventing the regular release and metabolism of normally efficacious antireflux therapies.

Gastroparesis and GERD Therapies

According to the American Gastroenterological Association (AGA) guidelines for gastroparesis, the primary therapy indicated for gastroparesis is dietary manipulation combined with the administration of prokinetic and antiemetic agents.[4] Prokinetic agents are used to induce gastric motility, whereas antiemetic agents are used to relieve symptoms of nausea and vomiting. Refractory gastroparesis may be treated by alternating prokinetic and antiemetic agents, combining therapies, or attempting some of the alternate therapies described in the next section.[4]

GERD occurs when the esophageal lining is exposed to excessive gastric acid, largely due to inappropriate transient relaxation of the lower esophageal sphincter. The American College of Gastroenterology (ACG) practice guidelines for GERD[5] characterize symptoms of heartburn and regurgitation as highly specific, particularly when experienced after large, fatty meals. GERD can be confirmed endoscopically by visual evidence of acid damage to the esophageal lining or pH testing demonstrating abnormal esophageal acid exposure. Additional symptoms indicating more complicated disease include dysphagia, odynophagia, weight loss, and anemia. GERD can ultimately lead to erosive esophagitis or Barrett esophagus. Therapy with proton pump inhibitors (PPIs) has provided the greatest efficacy in controlling GERD symptoms and healing esophagitis but the guidelines stress appropriate dosing before meals as key to success with PPI therapy. Delayed gastric emptying has been linked to GERD pathophysiology and refractory GERD.[6] As a result, promotility agents, such as metoclopramide, are commonly utilized in conjunction with PPIs.[5]

Therapeutic Challenges

One of the main challenges associated with the treatment of patients with gastroparesis and GERD is that the presence of one condition may prevent or complicate the standard treatment of the other condition. In patients with GERD refractory to standard therapy, a higher index of gastroparesis suspicion is recommended.[7] In addition, the presence of either or both of these conditions can impact the treatment of other comorbidities.[8] For example, gastroparesis may affect a diabetic patient's ability to adequately maintain their glucose levels.

Gastroparesis

Gastroparesis is commonly associated with symptoms such as early satiety, epigastric discomfort, nausea, and vomiting. In some patients, symptoms may result in decreased oral intake of all foods, resulting in malnutrition.[9] Additionally, patients

may develop an inability to tolerate orally administered medications because of esophageal dysmotility, which often develops in diabetic patients.[10] In particular, this may result in worsening patients other comorbidities, which require the administration of other medications to adequately control their natural course. Patients with diabetic gastroparesis have been shown to have a high prevalence of increased systemic cholecystokinin, which has been linked to esophageal dysmotility.[11] This dysmotility can lead to difficulty in tolerating orally administered medications, decreased compliance with oral antidiabetic regimens, and, ultimately, poor glycemic control. Orally administered medications may also demonstrate a marked increase in residence rate once in the stomach of patients with gastroparesis. This has the potential to significantly affect the pharmacodynamics and pharmacokinetics of the drug, resulting in changes in efficacy. Patients with Parkinson's disease frequently experience gastrointestinal dysfunction, including gastroparesis, which may lead to erratic absorption of drugs.[12]

GERD

The presence of gastroparesis, GERD, and potential associated dysphagia, may affect compliance with orally administered therapies.[13,14] Symptoms commonly associated with gastroparesis or GERD, including nausea, vomiting, and regurgitation, may delay drug absorption even in the event that the patient is able to swallow their medication. This has the potential to greatly impact systemic absorption and serum levels of drugs, and can greatly dissociate the time of administration from the time of ultimate drug effect. As noted above, optimal efficacy of PPIs requires coordination of drug release with mealtimes, in order to affect proton pumps at the times that they are most active.[15]

Refractory GERD is diagnosed in patients who are unresponsive to PPI treatment that has been administered for 4 to 8 weeks, once daily.[16] Patients with refractory GERD typically need more aggressive acid suppressive therapy or the use of other therapeutic modalities like transient lower esophageal sphincter relaxation reducers and, in the case of gastroparesis, co-administration of prokinetic agents to regulate gastric emptying. The optimal treatment of these patients remains to be determined, and there are no well-established guidelines specifically focusing on this condition. However, existing recommendations suggest these patients should undergo impedance and pH testing to exclude weakly acid reflux.[7] Those patients with normal impedance and pH may likely have functional heartburn as the underlying cause of their symptoms.

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Medical Options for the Treatment of Gastroparesis-Related GERD

Richard W. McCallum, MD

Treatment of gastroesophageal reflux disease (GERD) may benefit from the acknowledgement and treatment of underlying conditions, including gastroparesis. In addition to classical symptoms such as heartburn and regurgitation, patients with GERD often present with a variety of other symptoms. Thus it remains difficult to identify the particular subset of GERD patients who have gastroparesis, particularly if patients do not report classic symptoms of gastroparesis, including bloating, nausea, vomiting, and early satiety, or these symptoms are misinterpreted as GERD-related. Therefore, it is important that gastroparesis be considered in all patients with GERD, allowing physicians to develop an optimal therapeutic strategy that addresses both disease states directly.

Impact of GERD Medications on Gastric Motility

A number of first- and second-line therapies are available to treat GERD. The potential impact of these agents, either positive or negative, on gastric emptying is not well studied. However, evidence suggests that proton pump inhibitors (PPIs) may delay gastric emptying. Two small studies in healthy volunteers found that the PPI rabeprazole delayed gastric emptying.[1,2] Another trial in healthy participants reported that the PPI omeprazole also delayed gastric emptying.[3] Therefore, GERD patients with suspected gastroparesis should be advised to stop taking PPIs at least three days prior to a standard gastric emptying study, based on the pharmacology of PPI agents, in order to ensure that the test results reflect the true rate of gastric emptying. H_2 receptor antagonists, which enhance the release of acetylcholine, accelerate gastric emptying.[4-6] This is especially relevant because H_2 receptor antagonists are often taken in the evening in an effort to decrease nocturnal breakthrough of stomach acid and reduce nighttime symptoms. An evening dose of an H_2 receptor antagonist may unwittingly result in an improvement in the gastric emptying of the evening meal. Whether this strategy could have any meaningful effect on underlying gastroparesis is unknown.

Baclofen, a second-line therapy for GERD, is used to block transient relaxations of the lower esophageal sphincter. A randomized, double-blind study of 30 children showed that baclofen significantly increased the rate of gastric emptying compared with placebo.[7] However, this effect has not yet been studied and investigated in adults.

Gastroparesis and PPI Absorption

The administration of PPI agents is typically recommended 30–60 minutes prior to a meal. This time frame was chosen based on studies using a wireless indigestible capsule, which showed that transit time through an empty stomach is completed within 30–60 minutes.[8] The possibility of administering an agent more than 1 hour prior to consuming a meal has also been explored as an approach to maximize the chance of the tablet being absorbed in a fasting state, by providing more time for gastric emptying. However, these recommendations are made based on function in healthy subjects or in GERD patients with no complicating symptoms of dysphagia or presumed underlying gastroparesis. Both esophageal and gut transit can be altered in patients with complicated disease and may affect pill absorption significantly, thereby preventing optimal systemic concentration of PPI in the post-meal setting, when gastric acid production is being increased.

Several alternatives to the traditional tablet formulation of PPI agents have been developed to facilitate administration and drug delivery. [9] Lansoprazole is available in an orally dissolving tablet formulation, whereas omeprazole is available as an immediate release formulation that allows reconstitution with water to form an oral suspension. Because these medications work on an immediate-release basis, it can be assumed that they have the ability to overcome a delay in gastric emptying. These formulations may not necessarily be rapidly absorbed in the sublingual oral mucosa. However, they do provide the benefit of being immediately and initially dissolved in the mouth, overcoming the concern of patients who experience nausea or have a history of difficulty swallowing tablets.

Several patient populations may benefit from the use of medication formulations that offer an alternative to swallowing a traditional tablet (Table 1). Patients who are nauseated may appreciate an alternative to avoid swallowing a tablet with liquid. These alternative formulations may also be beneficial in patients who have odynaphagia, or painful swallowing, that could be exacerbated by taking a tablet. Patients with limited swallowing capacity, such as those with Parkinson's disease or other disorders of the central

Table 1. General Indications for Sublingual or Orally Dissolving Tablet Formulations

- Severe nausea or vomiting
- Swallowing difficulties (eg dysphagia, odynophagia)
- Medical conditions that impair swallowing (stroke, Parkinson's disease, etc.)
- Elderly and pediatric patients
- Patients with mental/psychological disease, dementia

Table 2. Nonsurgical Options for Gastroparesis-related Acid Reflux, Nausea, and Vomiting

- Prokinetics
- Antiemetics
- Motilin receptor antagonists
- 5-HT4 receptor agonists
- Gastric electrical stimulation
- GABA receptor agonists*
- Ghrelin agonists*

*Research on-going

nervous system, including poststroke problems, may also benefit from alternative formulations of PPIs. Elderly, weak, or bedridden patients could also benefit. These alternative formulations may also increase compliance in patients who are considered somewhat uncooperative, such as pediatric patients or individuals experiencing psychiatric episodes.

Treatment Options for Gastroparesis

The overall goals of treatment of gastroparesis are to correct deficiencies in fluids, electrolytes, and nutrition, identify and rectify the underlying cause of the gastroparesis, and reduce symptoms.[10] The most commonly used drug classes to treat gastroparesis include the prokinetic and antiemetic agents (Table 2). However, few large and well-powered clinical studies have been conducted to compare the efficacy of these treatments. Therefore, the majority of therapeutic recommendations are based on cumulative and empiric clinical experience.

Prokinetic drugs, such as metoclopramide, are used in the first-line treatment of gastroparesis. Overall, these agents improve the contractility of the gut muscles, as well as the movement of contents through the gastrointestinal system. Prokinetic agents also work to enhance antral contractility, correct gastric dysrhythmias, and improve antral-duodenal coordination. However, because the symptomatic response to prokinetic agents does not correlate well with actual gastric emptying, response to treatment is usually measured through clinical follow-up instead of serial gastric emptying tests.[11] The prokinetic metoclopramide is often administered as first-line therapy for gastroparesis, and has both prokinetic and antiemetic properties.[12] The prokinetic effect of metoclopramide is localized to the proximal gastrointestinal tract, where it increases esophageal, fundic and antral contractions, elevates lower esophageal sphincter pressure, and improves antropyloroduodenal coordination. Metoclopramide is approved by the US Food and Drug Administration (FDA) for the treatment of diabetic gastroparesis as well as GERD, and clinical trials show that it is effective in treating patients with idiopathic, diabetic, and post-surgical gastroparesis.[10] Aside from an oral tablet, other formulations of metoclopramide include intravenous, oral liquid, subcutaneous, and suppositories. In 2009, an orally disintegrating tablet formulation of metoclopramide was also approved. A randomized study in healthy volunteers showed that the pharmacokinetics of oral disintegrating tablets was similar to that of the conventional metoclopramide tablet.[13]

Metoclopramide (Table 3) is generally administered as a 10-mg dose up to 3–4 times daily. Side effects are associated with metoclopramide, restricting its use in nearly one-third of patients.[10] Approximately 10% of patients experience drowsiness and fatigue, whereas up to 6% of patients may experience acute dystonic reactions including facial spasm, oculogyric crisis, trismus, and torticollis. Other side effects include both physical and mental restlessness, agitation, and irritability, and it is possible that metoclopramide can aggravate underlying depression. The majority of these side effects occur relatively soon (within the first 1–2 weeks) after initiating therapy and generally resolve when metoclopramide is discontinued. In 2009, a black box warning was added for metoclopramide, reflecting an increased risk of tardive dyskinesia with long-term or high-dose use.[14] Therefore, metoclopramide is not recommended for use in patients with Parkinson's disease.[10] Due to the risk of significant side effects which may occur with chronic or high-dose administration of metoclopramide, it is critical that patients prescribed this agent be carefully and routinely followed by a clinician.

Erythromycin is a macrolide antibiotic that has been administered off-label as an alternative or adjunct to metoclopramide. Erythromycin appears to have prokinetic activity that is attributed to its activation of the motilin receptors located on gastroduodenal cholinergic neurons.[15,16] Erythromycin has been evaluated in diabetic, idiopathic, and post-surgical gastroparesis,[10] and several formulations of erythromycin are available.[17, 18] When administered orally, erythromycin is generally initiated at a dose of 125–250 mg 3–4 times daily as a tablet or pediatric syrup. However, erythromycin is more potent when administered intravenously, as is used for patients who require hospitalization.[19] An orally available liquid suspension is also available. The

Table 3. Metoclopramide

- Indicated for gastroparesis and symptomatic (refractory) GERD
- Increases lower esophageal sphincter pressure, accelerates gastric emptying, and coordinates GI activity
- Doses 10–15 mg q.i.d. for up to 12 weeks
  - 30 minutes before each meal and at bedtime
- Available in
  - Liquid: IV or IM injection
  - Tablet: 5 or 10 mg
  - Orally disintegrating tablet
- Onset of action
  - 1 to 3 minutes after IV dose
  - 10 to 15 minutes after IM injection
  - 30 to 60 minutes after oral tablet dose
- Pharmacological effects persist for 1 to 2 hours

GERD=gastroesophageal reflux disease; GI=gastrointestinal; IV=intravenous; IM=intramuscular.

long-term use of erythromycin is unpredictable due to dose tolerance and, hence, loss of response.

Antiemetic agents are an important component of gastroparesis therapy, and may be used to supplement prokinetic agents. The dopamine receptor antagonist phenothiazines (including prochlorperazine, trimethobenzamide, and promethazine) are frequently used, although side effects such as sedation and extrapyrimadal effects can occur. Other classes of antiemetics include serotonin receptor antagonists (ondansetron, granisetron, and dolasetron), antihistamines (diphenhydramine, dimenhydrinate, and meclizine), benzodiazepines (lorazepam and diazepam), and cannabinoid drugs (tetrahydrocannabinol).

A pyloric Botulinum toxin injection has been investigated as a potential alternative treatment for both diabetic and idiopathic gastroparesis. Its use as an inhibitor of neuromuscular transmission is based on evidence showing that patients with gastroparesis experience pylorospasm, or prolonged periods of increased pyloric tone and phasic contractions.[20] Botulinum toxin for gastroparesis, administered via pyloric injection, has been evaluated in multiple open label clinical studies, as well as blinded, randomized controlled studies.[10] These trials showed no benefit clinically beyond that seen with placebo. This treatment may result in mild improvements in gastric emptying and modest reductions in symptoms. Patients receiving botulinum toxin for gastroparesis have also reported side effects including injection-site reaction and prolonged dysphagia.

Gastric electrical stimulation has recently emerged as a therapeutic alternative in patients with refractory gastroparesis.[21] A gastric electric neurostimulator has received FDA approval for the treatment of chronic, refractory nausea and vomiting resulting from idiopathic or diabetic gastroparesis. This implantable neurostimulator delivers a high frequency, low energy signal in short pulses to stimulate the stomach. The efficacy of this intervention has been shown in one double blind trial and further studies are awaited.[21] Several open-label clinical trials have shown good longterm efficacy.[22]

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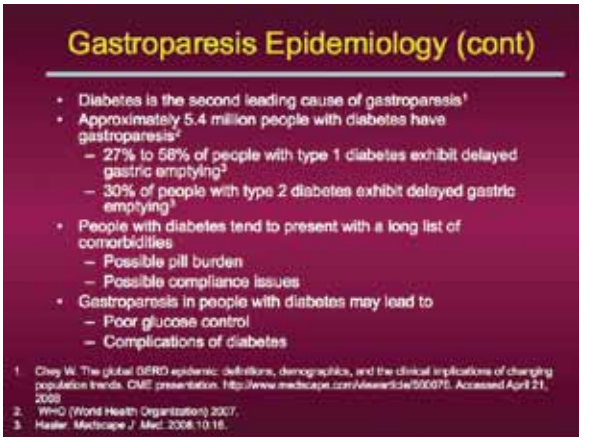

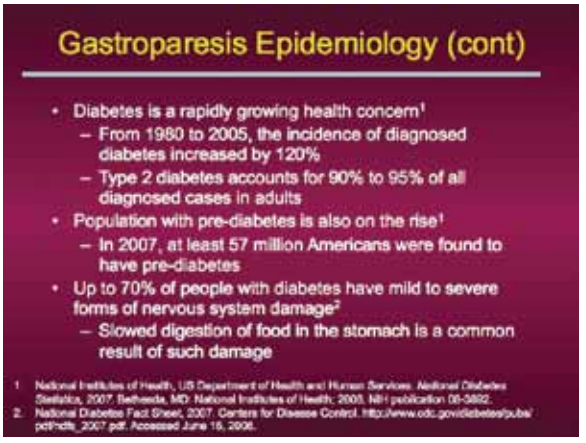

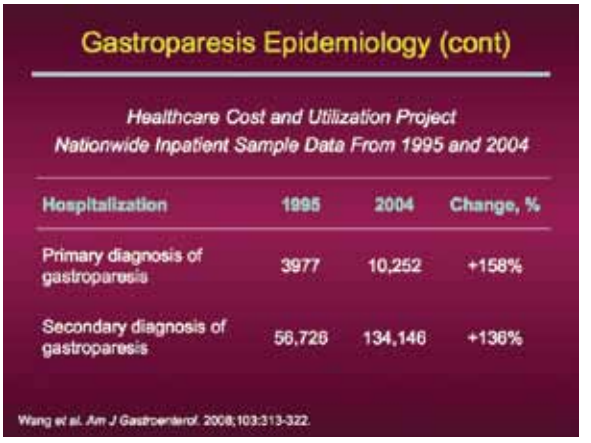

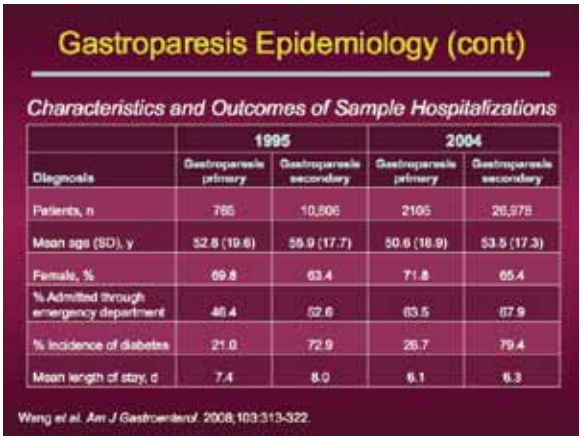

Gastroparesis Treatment Guidelines

- Primary treatment: dietary manipulation and administration of antiemetic and prokinetic agents
  - Antiemetics administered for nausea and vomiting
  - Serotonin (5-HT_3) receptor antagonists administered for prevention of chemotherapy-induced nausea and vomiting; best used on as-needed basis
  - Prokinetics (metoclopramide and erythromycin) can be administered orally or intravenously
- For refractory gastroparesis
  - Switch prokinetic and antiemetic agents; combine prokinetic agents; inject *Clostridium botulinum* toxin* into pylorus; use gastrostomy tubes; implant gastric electric stimulator

*Long-term control is not to be expected from this treatment.

Parkman et al, and the American Gastroenterological Association. Gastroenterology. 2004;127:1589-1591.

Metoclopramide

- Indicated for gastroparesis and symptomatic (refractory) GERD
- Increases lower esophageal sphincter pressure, accelerates gastric emptying, and coordinates GI activity
- Because of its peripheral antidopaminergic activity, CNS adverse events can occur
  - Somnolence, lethargy, anxiety, depression
  - Movement disorders (eg, akathisia, dystonia, tardive dyskinesia)
- MOA: prokinetic/promotility product

CNS = central nervous system; MOA = mechanism of action.

Pharmacokinetic Parameters (n=41)

Parameter	Rapidly disintegrating metoclopramide tablet, mean ± SD	Conventional metoclopramide tablet, mean ± SD
AUC_{inf}, ng•h/mL	245.7 ± 63.2	254.1 ± 71.4
AUC_{0-t}, ng•h/mL	267.6 ± 72.6	277.7 ± 85.2
C_{max}, ng/mL	27.9 ± 7.4	30.4 ± 7.2
T_{max}, h	1.8 ± 0.8	1.6 ± 1.2
$t_{½}$, h	6.4 ± 1.2	6.2 ± 1.3
K_{el}, 1/h	0.112 ± 0.02	0.115 ± 0.02

AUC_{inf}, area under the plasma concentration-time curve from time zero to infinity; AUC_{0-t}, area under the plasma concentration-time curve from time zero to the last quantifiable timepoint; C_{max}, peak plasma concentration; K_{el}, elimination rate constant; SD, standard deviation; $t_{½}$, elimination half-life; T_{max}, time to peak plasma concentration.

Data from Fass R, Pleniaszek HJ, Thompson JR. *Aliment Pharmacol Ther.* 2003;20:301-306.

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Notes

Treatment Challenges in the Management of Gastroparesis-Related GERD

CME Post-Test: *Circle the correct answer for each question below.*

1. The overall prevalence of gastroparesis is higher in_____.

   a. men
   b. women
   c. neither men or women; they are affected equally

2. Which of the following is NOT a common etiology of gastroparesis onset?

   a. Poorly controlled diabetes mellitus
   b. Postoperative onset following fundoplication surgery
   c. Withdrawal reaction upon completion of a course of systemic antibiotics
   d. Idiopathic gastroparesis of no discernable underlying cause

3. According to a study by McCullum and colleagues, ___ of GERD patients also had delayed gastric emptying.

   a. 41%
   b. 45%
   c. 58%
   d. 60%

4. According to the AGA, what constitutes the primary therapy for gastroparesis, along with prokinetic and antiemetic agents?

   a. proton pump inhibitors
   b. bulking agents
   c. dietary manipulation
   d. systemic antibiotics

5. Heartburn as a symptom of GERD is likely to occur after_____.

   a. extended fasting
   b. a large, fatty meal
   c. a full night's sleep
   d. exposure to freezing temperatures

6. Dosing and systemic release of proton pump inhibitors should be timed to coincide with _____.

   a. meals
   b. aerobic exercise
   c. symptom onset
   d. bowel movements

7. H2 receptor antagonists have been found to _____ gastric emptying.

   a. accelerate
   b. slow
   c. have no effect on

8. TRUE or FALSE: metoclopromide has both prokinetic and antiemetic properties.

   a. True
   b. False

9. The pharmacologic effects of a single dose of metoclopromide persist for_____.

   a. 8 hours
   b. 6 hours
   c. 3–4 hours
   d. 1–2 hours

10. Patients receiving pyloric Botulinum toxin injection have reported which of the following side effects?

    a. Rash
    b. Drowsiness
    c. Prolonged dysphagia
    d. Swollen lymph nodes

Evaluation Form

Treatment Challenges in the Management of Gastroparesis-Related GERD

PIM is committed to excellence in continuing education, and your opinions are critical to us in this effort. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgment for completing this activity.

Please rate your level of agreement by circling the appropriate rating:
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

Learning Objectives

After participating this activity, I am now better able to:

1. Describe the pathophysiologic relationship between gastroparesis and GERD symptoms. 1 2 3 4 5
2. Summarize the medical and surgical options for direct treatment of gastroparesis to relieve symptoms of reflux, nausea, and vomiting. 1 2 3 4 5
3. Describe the special needs of patients with gastroparesis and functional swallowing disorders and the best ways to address them when administering therapy. 1 2 3 4 5

Based upon your participation in this activity, choose the statement(s) that apply:

❒ I gained new strategies/skills/information that I can apply to my area of practice.
❒ I plan to implement new strategies/skills/information into my practice.

What strategies/changes do you plan to implement into your practice? _____

_____

What barriers do you see to making a change in your practice? _____

_____

Which of the following best describes the impact of this activity on your performance?

❒ I will implement the information in my area of practice.
❒ I need more information before I can change my practice behavior.
❒ This activity will not change my practice, as my current practice is consistent with the information presented.
❒ This activity will not change my practice, as I do not agree with the information presented.

Please rate your level of agreement by circling the appropriate rating:
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

The content presented:

Enhanced my current knowledge base 1 2 3 4 5
Addressed my most pressing questions 1 2 3 4 5
Promoted improvements or quality in health care 1 2 3 4 5
Was scientifically rigorous and evidence-based 1 2 3 4 5
Avoided commercial bias or influence 1 2 3 4 5

Would you be willing to participate in a post-activity follow-up survey? ❒ Yes ❒ No

Please list any topics you would like to see addressed in future educational activities: _____

_____

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Post-test Answer Key

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