Upper GI Disorders: Pathophysiology and Current Therapeutic Approaches

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B. Greenwood-Van Meerveld (ed.), *Gastrointestinal Pharmacology*,
Handbook of Experimental Pharmacology 239, DOI 10.1007/164_2016_114

Abstract

Symptoms referable to the upper digestive tract are associated with abnormalities of upper gastric neuromuscular function including abnormalities of motility, sensation, and absorption. Of the upper digestive tract, the stomach is of particular importance in its role in symptom generation and is highlighted in this chapter. Gastric symptoms can be associated with alterations in the rates of gastric emptying, impaired accommodation, heightened gastric sensation, or alterations in gastric myoelectrical activity and contractility. Treatment of gastric neuromuscular disorders requires an understanding of pathophysiology of the disorders, the appropriate use and interpretation of diagnostic tests, and the knowledge of effective treatment options. This chapter covers the pathophysiology and current treatment approaches to disorders of the upper gastrointestinal tract, focusing on classic disorders of the stomach, particularly gastroparesis and functional dyspepsia.

Keywords

Dumping syndrome • Functional dyspepsia • Gastroparesis

1 Introduction

Symptoms referable to the upper digestive tract are associated with abnormalities of upper gastric neuromuscular function including abnormalities of motility, sensation, and absorption (Boeckxstaens et al. 2016). The stomach is of particular importance in the upper digestive tract. Gastric symptoms can be associated with alterations in the rates of gastric emptying, impaired accommodation, heightened gastric sensation, or alterations in gastric myoelectrical activity and contractility (Parkman and Jones 2009). Treatment of gastric neuromuscular disorders requires an understanding of pathophysiology, appropriate use and interpretation of diagnostic tests, and treatment options (Parkman et al. 1995; Camilleri et al. 1998). These tests include measures of gastric emptying, contractility, electrical activity, regional gastric motility of the fundus, antrum, pylorus, and tests of sensation and compliance. In addition to these gastric function tests, tests are being developed to help better understand the afferent sensory pathways from the stomach to the central nervous system that mediate gastric sensation. This chapter covers the pathophysiology and current treatment approaches to disorders of the upper gastrointestinal tract, focusing on gastric disorders, particularly the classic gastric disorder of gastroparesis.

2 Normal Gastric Neuromuscular Physiology

Normal gastric physiology is best described in terms of its patterns in the fasting state and the responses of the stomach that occur in response to food intake (the fed response) (Camilleri et al. 1998; Camilleri 2006).

2.1 Fasting Gastric Motility

Fasting gastric contractile patterns are characterized by a cyclic motor phenomenon called the migrating motor complex (MMC) (Camilleri et al. 1998). In healthy people, it occurs approximately once every 90 min in the fasting state, most prominently at night. The fasting state generally starts approximately 4 h after meal ingestion when the stomach has completely emptied a meal. The fasting contractile patterns comprise a period of quiescence (phase I), a period of intermittent pressure activity (phase II), and an activity front, during which the stomach and small intestine contract at their highest frequency (phase III). During the phase III MMC, contraction frequencies reach 3 per minute in the stomach and 12 per minute in the proximal small intestine. This interdigestive contraction wave migrates down the stomach and small intestine and serves to help empty the stomach of indigestible solids and transport them down the small intestine into the colon ("the intestinal housekeeper"). These contractile pressures, especially in the fasting period, are generally recorded in patients with antroduodenal manometry.

2.2 Gastric Responses to Meal Ingestion

2.2.1 Gastric Accommodation

Gastric accommodation is a postprandial, vagally mediated reflex resulting in reduced gastric tone primarily in the proximal stomach that occurs with eating a meal (Cannon and Lieb 1911). Gastric accommodation provides a reservoir for ingested foods without a significant increase in intragastric pressure.

The accommodation reflex has two principal components. *Receptive relaxation* occurs within seconds of eating and is triggered by both oropharyngeal and gastric stimulation. This response involves relaxation of both the lower esophageal sphincter and proximal stomach. *Adaptive relaxation* is a slower process triggered by gastric or duodenal distension and perhaps also modified by specific nutrients (Villanova et al. 1997; Jahnberg et al. 1975). The accommodation reflex is vagally mediated and represents the balance between cholinergic excitatory drive and non-adrenergic non-cholinergic (NANC) inhibitory input. The afferent signal is generated by activation of stretch-sensitive mechanoreceptors in the stomach wall and by activation of osmo- and chemoreceptors in the stomach and duodenum (Feinle et al. 2001). The efferent NANC signal involves nitric oxide (NO) as the principal neurotransmitter (Boeckxstaens et al. 2002; Tack et al. 2002a) and perhaps vasoactive intestinal polypeptide (VIP) (Tonini et al. 2000). Gastric tone is also modulated by sympathetic inputs acting directly through post-junctional α1-adrenoceptors, and indirectly on cholinergic nerve terminals mediated by pre-junctional α2-adrenoceptors (Boeckxstaens et al. 2002; Tack et al. 2002a; Thumshirn et al. 1999a).

The accommodation reflex is most often recorded using either a gastric barostat or imaging methods such as scintigraphic radiolabelling of the gastric mucosa with the use of single-photon emission computed tomography (SPECT). The roles for various nutritional parameters in modifying accommodation such as meal volume and rate of ingestion, caloric density, and macronutrient content require more understanding as this might have important clinical relevance.

2.2.2 Gastric Emptying of a Meal

Normal gastric emptying reflects a coordinated effort between the fundus, antrum, pyloric sphincter, and duodenum (Parkman et al. 1995; Camilleri et al. 1998). Coordination of these fundic-antral-pyloric-duodenal motor events is carefully regulated and governed by gastrointestinal electrical activity through the interstitial cells of Cajal (ICCs) and neural connectivity through enteric nerves and vagal efferent nerves from the central nervous system. Feedback from nutrients and volume in the stomach and small bowel impact the process of gastric emptying and are conveyed through local enteric sensory nerves, vagal afferent nerves, and hormones.

Fundic and antral smooth muscle contractions are primarily cholinergically mediated. Rhythmic antral contractions, classically at 3 cycles/minute, triturate large food particles into an appropriate size for intestinal digestion. The rate of these contractions is governed by the electrical pacemaker area of the stomach and the pacemaker cells, the interstitial cells of Cajal (ICCs).

Pyloric sphincter relaxation, often synchronized with antral contractions, allows smaller food particles and chyme to pass out of the stomach into the duodenum (Camilleri et al. 1998). Pyloric relaxation is mediated through release of inhibitory nerves, especially nitric oxide (NO) and possibly vasoactive intestinal polypeptide (VIP).

Solid and liquid food empty from the stomach at different rates (Camilleri et al. 1998). Liquids empty from the stomach at an exponential rate as their emptying depends primarily on the gastric–duodenal pressure gradient with less importance on pyloric opening. Solids are initially retained selectively within the stomach until particles have been triturated to a size smaller than 2 mm, at which point they can be emptied at a linear rate from the stomach.

2.3 Gastric Sensation

The digestive tract senses ingested meals in various ways (Parkman and Jones 2009). Volume, osmolarity, acidity, and macronutrient composition represent the dominant sensory modalities. Most of this sensory information is acted upon solely by the enteric nervous system to facilitate secretion, absorption, and motility through the gut and never reaches the level of consciousness. Some awareness of digestive sensation such as fullness and satiation helps regulate normal eating behavior. Visceral sensation is transmitted from the digestive tract to the central nervous system primarily via the vagus nerve and spinal afferent system.

Afferent vagal neurons project mainly to the solitary tract nucleus with secondary projections ascending to the thalamus and directly to other brain structures involved in arousal, homeostatic, and emotional behaviors (Sawchenko 1983; Aziz and Thompson 1998). These regions include the hypothalamus, locus coeruleus, amygdala, and periaqueductal gray (PAG). Third-order neurons project from the thalamus to the sensory cortex.

Primary spinal visceral afferent nerves synapse in the dorsal horn of the spinal cord with secondary neurons projecting proximally through the spinoreticular, spinomesencephalic, spinohypothalamic, and spinothalamic tracts (Almeida et al. 2004; Drossman

2004; Jones et al. 2006). Spinoreticular inputs activate reflexive responses to visceral sensation without conscious awareness. The spinothalamic tract projects to the ventral posterior lateral, medial dorsal, and ventral medial posterior nuclei of the sensory thalamus, from which tertiary neurons relay digestive sensory signals to the primary somatosensory cortex (S1 and S2), the cingulate cortex, and the insula, respectively.

3 Gastric Symptoms and Pathophysiology

Symptoms may originate by four types of pathophysiological mechanisms: delayed gastric emptying, impaired accommodation, increased perception (hypersensitivity), or accelerated gastric emptying (Table 1) (Boeckxstaens et al. 2016). This has recently been elegantly reviewed by Azpiroz and colleagues for Rome IV Pathophysiology (Boeckxstaens et al. 2016) and is discussed in this section. The symptoms from gastric dysfunction are limited and the symptoms may be similar in character regardless of the underlying pathophysiological mechanisms involved.

3.1 Delayed Gastric Emptying

Gastric emptying reflects the net output of the stomach, which is regulated by three areas of the stomach: proximal fundus, distal antrum, and pyloric sphincter (Malagelada and Azpiroz 1989). Neural and hormonal pathways from the small intestine also influence gastric emptying. The tonic contraction of the proximal stomach pushes gastric contents distally into the antrum. Impaired tonic contraction of the proximal stomach may result in a delay in the emptying of both solids and liquids. Phasic antral contractions produce the breakdown of solid particles necessary for passage through the pylorus into the small intestine; impaired antral contractions result in the delayed emptying of solids (Camilleri et al. 1998).

Delayed gastric emptying produces symptoms especially from retention of food or chyme in the stomach. The symptoms vary from mild symptoms such as early satiety, epigastric fullness, and nausea to severe manifestations with vomiting of food, often

Table 1 Pathophysiology involved in gastric disorders

Delayed gastric emptying
Gastroparesis
Functional dyspepsia
Impaired accommodation
Functional dyspepsia
Rapid gastric emptying
Dumping syndrome
Cyclic vomiting syndrome
Post fundoplication
Functional dyspepsia
Increased perception/hypersensitivity
Functional dyspepsia

ingested many hours or even days earlier, and nutritional compromise. Absence of fasting gastric phase III MMC activity may result in gastric bezoar formation. Interestingly, nausea and vomiting may occur in some patients during fasting rather than postprandially, especially seen in diabetic patients (Parkman et al. 2016). In some patients, this may lead to inability to eat from symptoms with resultant weight loss. Delayed gastric emptying in the absence of mechanical obstruction is the definition of the disorder gastroparesis (Grover et al. 2012; Janssen et al. 2013). Some patients with functional dyspepsia exhibit a delay of solid emptying.

3.2 Impaired Accommodation

Impaired accommodation of the proximal stomach in response to food ingestion increases gastric wall tension which might activate sensory endings in the gastric wall and produce symptoms. Inappropriate relaxation might be related to impaired enterogastric and antrofundic reflexes that normally modulate the gastric accommodation/emptying process (Azpiroz and Malagelada 1987; Farre and Tack 2013). Impaired fundic accommodation/reduced proximal gastric relaxation in response to a meal can be seen in some patients with functional dyspepsia and has been reported to be associated with early satiety and weight loss (Tack et al. 2001). Impaired accommodation is associated with abnormal intragastric distribution of food in patients with functional dyspepsia, with preferential accumulation in the distal stomach (antrum) (Troncon et al. 1994).

3.3 Increased Gastric Sensitivity

Distending the stomach can produce conscious sensations similar to the symptoms reported by patients with gastric functional disorders. Perception of gastric distension depends on activation of tension rather than elongation or volume receptors in the gastric wall (Distrutti et al. 1999). Some patients with functional dyspepsia exhibit increased perception of gastric distension or hypersensitivity of the stomach (Coffin et al. 1994). Gastric hypersensitivity is more prevalent in patients with predominant epigastric pain (Karamanolis et al. 2006). Gastric hypersensitivity can coexist with impaired gastric accommodation to meal ingestion and delayed gastric emptying.

The cause and mechanism of gastric hypersensitivity are not known. In normal conditions, gastric sensitivity is modulated by several mechanisms. For example, lipids in the small intestine increase perception of gastric distension. This modulatory mechanism is up-regulated in patients with functional dyspepsia, and may contribute to symptoms. Altered perception in a subset of patients with dyspepsia appears to occur as a consequence of an acute, possibly viral, gastroenteritis, which leads to impaired nitrergic nerve function in the proximal stomach (Tack et al. 2002b). Central mechanisms may also play a role. For example, anxiety is negatively correlated with pain and discomfort threshold in hypersensitive functional dyspeptic patients (Van Oudenhove et al. 2007).

3.4 Accelerated Gastric Emptying

In some patients, mainly after partial or complete gastrectomy, rapid gastric emptying is accompanied by vasomotor and gastrointestinal symptoms. This dumping syndrome may be observed after vagotomy, intentional or unintentional at the time of surgery at the gastroesophageal junction. Symptoms typically occur after ingestion of liquids and meals with increased carbohydrates. Dumping symptoms can be subdivided into "early dumping" and "late dumping" symptoms. "Early dumping" occurs in the first hour after meal ingestion and is associated with both abdominal and systemic symptoms due to the rapid passage of hyperosmolar contents into the small bowel leading to a shift of fluids from the intravascular compartment to the gut lumen. This induces intestinal distension and gastrointestinal symptoms like bloating, abdominal pain, and diarrhea (Vecht et al. 1997). Enhanced release of several gastrointestinal hormones, including enteroglucagon, vasoactive intestinal polypeptide, peptide YY, pancreatic polypeptide, and neurotensin, are thought to cause a systemic and splanchnic vasodilation, most likely explaining the vasomotor symptoms. Late dumping occurs 1–2 h postprandially and results from reactive hypoglycemia. Rapid gastric emptying induces high glycemic levels, which lead to increased insulin secretion. Because of the long half-life of insulin, late reactive hypoglycemia may occur.

4 Disorders Associated with Altered Gastric Motility and Function

4.1 Gastroparesis

Gastroparesis is a symptomatic chronic disorder of the stomach characterized by delayed gastric emptying in the absence of mechanical obstruction. Symptoms of gastroparesis are variable and include early satiety, postprandial fullness, nausea, vomiting, abdominal distension, and upper abdominal discomfort (Parkman et al. 2004). Delayed gastric emptying is also common in functional dyspepsia, occurring in approximately 25–40% of patients (Stanghellini et al. 1996; Sarnelli et al. 2003).

The correlation between symptoms and delayed gastric emptying is variable (Horowitz et al. 1989; Koch et al. 1989; Talley et al. 1989). Postprandial fullness, nausea, and vomiting have been reported to predict delayed emptying in patients with functional dyspepsia (Stanghellini et al. 1996; Sarnelli et al. 2003). In patients with diabetes, abdominal fullness and bloating were found to predict delayed gastric emptying (Jones et al. 2001). In some drug trials of prokinetic agents, symptom improvement correlated with acceleration of gastric emptying (Camilleri et al. 1989; Jian et al. 1989); however, in other studies, this relationship has not been demonstrated (Snape et al. 1982; McCallum et al. 2007). In individuals with symptoms of gastroparesis who have normal rates of gastric emptying, other motor, myoelectric, or sensory abnormalities may elicit symptoms (Parkman et al. 1995). Perhaps different pathophysiology may explain different symptoms seen in upper GI disorders (Table 2).

Table 2 Relationship of gastric pathophysiologic alterations and symptoms

Pathophysiology	Associated symptoms
Delayed gastric emptying	Vomiting
	Postprandial fullness
Delayed proximal gastric emptying	Heartburn
	Regurgitation
Impaired proximal gastric accommodation	Early satiety
	Weight loss
Hypersensitivity	Abdominal pain
	Belching
	Weight loss
Gastric dysrhythmias	Nausea

Gastroparesis occurs in many clinical settings; idiopathic, diabetic, and postsurgical etiologies comprise the majority of cases in most series. In one series of 146 patients, gastroparesis was idiopathic in 36%, diabetic in 29%, and postsurgical in 13% of patients (Soykan et al. 1998). Several gastrointestinal and systemic diseases are associated with gastroparesis.

Delayed gastric emptying of solids after gastric surgery or vagal nerve injury is common with patients most commonly experiencing vomiting, weight loss, and bezoar formation. The incidence of postsurgical gastroparesis varies from 5 to 25% (Eagon et al. 1992). The dominant mechanism appears to be vagal injury with resultant loss of both fundal tone and antral peristalsis (Eagon et al. 1992).

4.2 Generalized Disorders of Gastrointestinal Motility

Gastroparesis may occur as a component of a generalized gut dysmotility syndrome. Chronic intestinal pseudo-obstruction is a syndrome with recurrent symptoms suggestive of intestinal obstruction in the absence of mechanical blockage. Radiologic findings of chronic intestinal pseudo-obstruction include luminal dilation with air-fluid levels throughout the small intestine. Chronic intestinal pseudo-obstruction can be caused by a variety of systemic diseases, including scleroderma, amyloidosis, myxedema, long-standing diabetes mellitus, and paraneoplastic complications most commonly seen with small-cell lung carcinoma. However, many cases are idiopathic in nature. The two main forms of chronic intestinal pseudo-obstruction are myopathic and neuropathic. Antroduodenal manometry may assist in differentiating these two forms (Camilleri et al. 1998). In intestinal myopathy, low-amplitude contractions that propagate normally are seen. In intestinal neuropathy, contractions are normal in amplitude but disorganized in morphology, including disruption of phase III activity, bursts of nonpropagating activity during fasting, and failure to convert from the fasting to the postprandial fed motor pattern.

4.3 Dumping Syndrome and Rapid Gastric Emptying

Dumping syndrome is characterized by rapid gastric emptying accompanied by gastrointestinal and vasomotor symptoms. It occurs mainly after partial or complete gastrectomy, vagotomy (often postsurgical but occasionally due to diabetes or dysautonomia), fundoplication, or bariatric surgery (Lee et al. 2007; Tack 2007). Symptoms result from rapid gastric emptying and are characterized into early and late dumping. Early dumping begins shortly after meal ingestion and is characterized by symptoms of epigastric fullness, crampy abdominal pain, nausea and vomiting, diarrhea, sweating, weakness, dizziness, pallor, palpitations, and tachycardia. Late dumping typically begins 90–240 min after a carbohydrate-rich meal and includes symptoms of diaphoresis, tremulousness, tachycardia, light-headedness, weakness, and confusion.

Symptoms of early dumping are explained in part by the rapid passage of hyperosmolar contents into the small bowel, accompanied by a shift of fluids from the intravascular compartment to the lumen (Vecht et al. 1997). This induces intestinal distention and accompanying symptoms. The vasomotor symptoms are due to enhanced release of gastrointestinal hormones resulting in splanchnic vasodilation and vascular pooling along with accompanying fluid shifts. Late dumping is attributed largely to reactive hypoglycemia following transient dumping-induced hyperglycemia with reactive insulin secretion. As the effects of insulin typically persist beyond the transient initial hyperglycemia, reactive glycemia occurs when all sugars have been absorbed.

Dumping syndrome is diagnosed based on clinical symptoms in a patient with predisposing conditions. Gastric emptying studies can demonstrate rapid gastric emptying (Jian et al. 1992). Gastric emptying of liquids focusing on the early phases of emptying may be particularly helpful as gastric emptying of solids is more variably affected. The diagnosis is confirmed by demonstrating hypoglycemia in association with postprandial symptoms.

Rapid gastric emptying of solids has been demonstrated in some patients with functional dyspepsia (Lin et al. 1999; Delgado-Aros et al. 2004) and has also been reported in diabetes, particularly early in the course of type II diabetes (Schwartz et al. 1996). Many of these patients have symptoms indistinguishable from those of gastroparesis. Rapid emptying has been recently observed as an accompanying factor in adult patients with cyclic vomiting syndrome (Namin et al. 2006; Fajardo et al. 2005).

4.4 Functional Gastroduodenal Disorders

According to Rome III and IV criteria, functional dyspepsia is defined as symptoms of bothersome postprandial fullness, early satiation, epigastric pain, and/or epigastric burning with no evidence of structural disease (Tack et al. 2006; Stanghellini et al. 2016). It has been suggested to categorize patients with functional dyspepsia as having pain-predominant symptoms (epigastric pain syndrome) or symptoms related to

the ingestion of a meal such as early satiation and postprandial fullness (postprandial distress syndrome).

There are associations of various dyspeptic symptoms with alterations in gastric emptying, accommodation, and sensitivity (Table 2); these associations are modest but inconsistent (Boeckxstaens et al. 2001, 2002; Tack et al. 2006; Talley et al. 2001). Nevertheless, there is evidence that gastrointestinal motility and sensation are disturbed in at least a subset of patients with functional dyspepsia. Delayed gastric emptying is reported in between 20 and 50% of patients with functional dyspepsia and a meta-analysis of 17 studies demonstrated significantly delayed solid-phase gastric emptying in 40% of patients with functional dyspepsia (Quartero et al. 1998). Several large studies have demonstrated that patients with delayed gastric emptying for solids are more likely to report postprandial fullness, nausea, and vomiting but these associations are not consistently confirmed (Stanghellini et al. 1996; Talley et al. 2001; Perri et al. 1998). Interestingly, in a series reported by Delgado-Anos et al., 17/39 (43%) of patients with functional dyspepsia had initial rapid gastric emptying at 1 h, whereas 16/39 (41%) patients had delayed overall gastric emptying at 4 h (Delgado-Aros et al. 2004). Symptoms did not differentiate those with delayed versus rapid gastric emptying.

There is some overlap between gastroparesis and functional dyspepsia as both symptoms and gastric emptying test results may meet definitions for both in a subset of patients (Parkman et al. 2004; Tack et al. 2006). As a consequence, some patients with mild abdominal pain, nausea, vomiting, and evidence of delayed emptying are considered to have functional dyspepsia by some clinicians and gastroparesis by others. Patients with marked delay in gastric emptying should be diagnosed with gastroparesis not functional dyspepsia. In general, predominant abdominal pain with lesser degrees of nausea is more consistent with a diagnosis of functional dyspepsia, whereas predominant nausea and vomiting with lesser degrees of abdominal pain are more characteristic of gastroparesis.

Using either a gastric barostat or a single-photon emission computed tomography (SPECT), impaired accommodation of the proximal stomach has been reported in up to 40% of patients with functional dyspepsia (Bredenoord et al. 2003; Thumshirn et al. 1999b). While associations have been reported between impaired gastric accommodation and symptoms of early satiety, these are not consistently confirmed (Boeckxstaens et al. 2002; Tack et al. 2001). Similarly, an association between hypersensitivity to gastric distention and symptoms of pain, belching, and weight loss has been reported (Tack et al. 2001; Salet et al. 1998). Again, while heightened sensitivity to gastric distension is commonly observed, symptom associations are not consistently demonstrated (Boeckxstaens et al. 2002; Salet et al. 1998). Additionally, it has been shown that state anxiety is significantly and negatively correlated with discomfort threshold, pain threshold, and compliance (Van Oudenhove et al. 2007). This observation highlights the complex relationships between pain and factors such as psychiatric distress and somatization.

5 Current Therapeutic Approaches to Upper GI Disorders, Particularly Gastroparesis

Management of upper gastrointestinal disorders, particularly gastroparesis, is guided by the goals of correcting fluid, electrolyte, and nutritional deficiencies; identifying and treating the cause of delayed gastric emptying (e.g., diabetes); and suppressing or eliminating symptoms (Camilleri et al. 1998). Care of patients generally relies on dietary modification, medications that stimulate gastric motor activity, and antiemetic drug therapy.

The outcome of patients with gastroparesis has not been well characterized. It is often felt by many clinicians to be a difficult disorder to treat, reflecting not only paucity of medications that are available for this condition, but also the incomplete understanding of the reasons for the symptoms. The outcome of gastroparesis patients was assessed in the NIH Gastroparesis Consortium in patients with either diabetic or idiopathic gastroparesis (Pasricha et al. 2015). Surprisingly, only 28% of 262 patients symptomatically improved at 48 weeks as determined by a decrease in GCSI $\geq$ 1. This illustrates the chronic nature of gastroparesis and that the disease burden remains high. Predictors for improvement included more severe gastroparesis symptoms, more severe delay in gastric emptying, and an initial infectious prodrome. Predictors for a poor improvement included moderate/severe abdominal pain and being overweight.

5.1 Dietary Treatment

Dietary measures entail adjustment to meal composition and frequency (Parkman et al. 1995; Moore et al. 1984). Eating small meals is recommended as patients often have early satiety, that is, feeling full when eating a normal size meal; in addition, larger meals may alter gastric emptying times. Consuming mainly liquids such as soups can be useful as gastric emptying of liquids is often preserved in patients with gastroparesis (Parkman et al. 1995). Avoidance of fats and indigestible fibers is recommended because they delay gastric emptying (Parkman et al. 1995). When small meals are used in the gastroparesis diet, more frequent meals, 3 meals/day plus 2 snack-type meals, are often needed to maintain caloric intake. These dietary recommendations have often been made empirically as to effects on gastric emptying (Moore et al. 1981, 1984). Recently, these have been looked at in respect to symptom generation. A high-fat solid meal significantly increased overall symptoms among individuals with gastroparesis, whereas a low-fat liquid meal had the least effect (Homko et al. 2015). With respect to nausea, low-fat meals were better tolerated than high-fat meals, and liquid meals were better tolerated than solid meals. These data provide support for recommendations that low-fat and increased liquid-content meals are best tolerated in patients with symptomatic gastroparesis. Another study assessed patient tolerances to foods (Wytiaz et al. 2015). Foods provoking symptoms were generally fatty, acidic, spicy, and roughage based. Foods worsening symptoms included orange juice, fried chicken, cabbage, oranges,

sausage, pizza, peppers, onions, tomato juice, lettuce, coffee, salsa, broccoli, bacon, and roast beef. The foods that were generally tolerable were generally bland, sweet, salty, and starchy. Saltine crackers, jello, and graham crackers moderately improved symptoms. Twelve additional foods were tolerated by patients (not provoking symptoms): ginger ale, gluten-free foods, tea, sweet potatoes, pretzels, white fish, clear soup, salmon, potatoes, white rice, popsicles, and applesauce.

Many patients with gastroparesis have diets deficient in calories, vitamins, and minerals. Unfortunately, nutritional consultation is obtained infrequently but this is suggested for dietary therapy and to address nutritional deficiencies (Parkman et al. 2011).

5.2 Glucose Control in Diabetic Patients

Diabetic patients with gastroparesis frequently exhibit labile blood glucose concentrations with prolonged periods of significant hyperglycemia. Hyperglycemia itself can delay gastric emptying. Hyperglycemia can counteract the accelerating effects of prokinetic agents on gastric emptying. Improvement of glucose control increases antral contractility, corrects gastric dysrhythmias, and accelerates emptying. To date, there have been no long-term studies confirming the beneficial effects of maintenance of near euglycemia on gastroparetic symptoms. Nevertheless, the consistent findings of physiologic studies in healthy volunteers and diabetic patients provide a compelling argument to strive for near-normal blood glucose levels in affected diabetic patients. Generally, patients give their mealtime insulin after ingesting the meal, to ensure that the entire anticipated meal is actually consumed and without vomiting.

In a recently reported multicenter pilot study (GLUMIT), continuous subcutaneous insulin infusion with insulin pump therapy with continuous glucose monitoring reduces hypoglycemia in diabetes with gastroparesis (Calles et al. 2015). There were also associated improvements in gastroparesis symptoms and nutrient tolerance benefits which were maintained for the 24-week phase of intensive monitoring and therapy. This pilot study shows the feasibility and potential for dual benefits improving both diabetes control and lowering gastroparesis symptom burdens.

5.3 Prokinetic Agents

Medications with gastric prokinetic properties, which are the mainstay of treatment for gastroparesis, include metoclopramide, erythromycin, and domperidone (McCallum and George 2001). Intravenous agents currently available to treat hospitalized patients include metoclopramide and erythromycin. Several prokinetic agents are being studied for patients with gastroparesis; these include newer 5-HT4 receptor agonists with less cardiac side effects, newer motilin receptor agonists with less tachyphylaxis phenomenon and without antibiotic properties, and newer ghrelin receptor agonists.

5.3.1 Metoclopramide

Metoclopramide, a substituted benzamide structurally related to procainamide, exhibits both prokinetic and antiemetic actions. The drug is a dopamine type 2 receptor antagonist both in the CNS and in the stomach. Metoclopramide also has 5HT-3 receptor antagonist activity that might also provide an antiemetic effect. In addition, it has some 5HT-4 agonist activity releasing acetylcholine from intrinsic myenteric cholinergic neurons that might help enhance gastric emptying. The prokinetic properties of metoclopramide are limited primarily to the stomach. Reglan can cause both acute and chronic CNS side effects in some patients. These side effects should be discussed with the patient prior to treatment and documented in the patient's medical record. In the USA, metoclopramide is approved for diabetic gastroparesis for up to 12-week duration. Patients with gastroparesis have chronic nausea and often need longer periods of treatment. Recently, in Europe, it has been suggested that metoclopramide be used for only several days' duration for acute treatment of chemotherapy-induced vomiting.

5.3.2 Erythromycin

The macrolide antibiotic erythromycin exerts prokinetic effects via action on gastroduodenal receptors for motilin, an endogenous peptide responsible for initiation of the migrating motor complex (MMC) in the upper gut. When administered exogenously, motilin stimulates antral contractility and elicits premature antroduodenal phase III activity. Erythromycin produces effects on gastroduodenal motility similar to motilin.

Clinically, erythromycin has been shown to stimulate gastric emptying in diabetic gastroparesis, idiopathic gastroparesis, and postvagotomy gastroparesis. Erythromycin may be most potent when used intravenously; it is often used to clear the stomach from blood prior to an upper endoscopy for a patient with upper gastrointestinal bleeding. Limited data exist concerning the clinical efficacy of erythromycin in reducing symptoms of gastroparesis. In a systematic review of studies on oral erythromycin with symptom assessment as a clinical end point, improvement was noted in 43% of patients. One study comparing erythromycin and metoclopramide in an open-label, crossover fashion in diabetic gastroparesis found similar efficacy.

Oral administration of erythromycin should be initiated at low doses (e.g., 100–125 mg 3 times daily before meals). Liquid suspension erythromycin may be preferred because it is rapidly and more reliably absorbed. Intravenous erythromycin (100 mg every 8 h) is used for inpatients hospitalized for severe refractory gastroparesis. Side effects of erythromycin at higher doses (500 mg) include nausea, vomiting, and abdominal pain. Because these symptoms may mimic those of gastroparesis, erythromycin may have a narrow therapeutic window in some patients. There is report that erythromycin chronically may be associated with higher mortality from cardiac disease, especially when combined with agents that inhibit cytochrome p-450, such as calcium channel blockers.

5.3.3 Domperidone

The effects of domperidone on the upper gut are similar to those of metoclopramide, including stimulation of antral contractions and promotion of antroduodenal coordination. In addition to prokinetic actions in the stomach, domperidone exhibits antiemetic properties via action on the area postrema, a brainstem region with a porous blood-brain barrier. Domperidone does not readily cross the blood-brain barrier; therefore, it is much less likely to cause extrapyramidal side effects than metoclopramide. Side effects to domperidone include breast lactation, headaches, and palpitations. Domperidone has been associated with prolongation of the cardiac QTc interval.

The FDA has developed a program for physicians who would like to prescribe domperidone for their patients with severe upper GI motility disorders that are refractory to standard therapy to open an Investigational New Drug Application (IND). An IND is a request for FDA authorization to administer an investigational drug to humans. Such authorization would allow the importation, interstate shipment, and administration of the drug even though it is not approved for sale in the USA. Use of this IND mechanism for use of domperidone also will require IRB approval. An EKG and blood work to check potassium and magnesium are obtained prior to starting domperidone; these are repeated after 4–8 weeks of treatment. The patient will need to pay for their domperidone medication since insurance companies do not for this nonapproved treatment.

The benefits and side effects of domperidone to treat symptoms of gastroparesis were recently reported from a large single-center cohort (Schey et al. 2016). In this large single-center study of 125 patients treated with domperidone, side effects necessitating discontinuing treatment occurred in 12%. The most common side effects were headache, tachycardia/palpitations, and diarrhea. The majority of patients (60%) experienced an improvement in symptoms of gastroparesis, particularly postprandial fullness, nausea, vomiting, and stomach fullness.

5.4 Antiemetic Medications

Antiemetic agents are given acutely for symptomatic nausea and vomiting. The principal classes of drugs that have been used for symptomatic treatment of nausea and vomiting are phenothiazines, antihistamines, anticholinergics, dopamine receptor antagonists, and more recently serotonin receptor antagonists. The antiemetic action of phenothiazine compounds appears to be mediated primarily through a central antidopaminergic mechanism in the area postrema of the brain. Commonly used agents include prochlorperazine (Compazine), trimethobenzamide (Tigan), and promethazine (Phenergan).

Serotonin (5-HT-3) receptor antagonists, such as ondansetron (Zofran) and granisetron (Kytril), have been shown to be helpful in treating or preventing chemotherapy-induced nausea and vomiting. The primary site of action of these compounds is probably the chemoreceptor trigger zone, since there is a high density of 5-HT-3 receptors in the area postrema. Zofran is now frequently used for nausea and vomiting of a variety of other etiologies. It is best given on a prn basis due to their expense. Granisetron

transdermal system (GTS) is an appealing delivery system for patients with gastroparesis. In an open-label study, GTS was moderately effective in reducing nausea and/or vomiting in 76% of gastroparesis patients (Midani and Parkman 2016). Side effects can occur such as constipation, skin rash from the patch, and headaches.

Neurokinin receptor antagonists are being used for chemotherapy-induced nausea and vomiting. Aprepitant (Emend) is a recently approved substance P/neurokinin 1 receptor antagonist for chemotherapy-induced nausea and vomiting. In a recent abstract presentation (Pasricha et al. 2016), the effects of the neurokinin-1 receptor antagonist aprepitant on symptoms in patients with gastroparesis (Gp) and related syndromes associated with chronic nausea and vomiting patients. Aprepitant resulted in a greater decline in mean 4-week daily hours of nausea and mean 4-week GCSI score. These data suggest that aprepitant has the potential for safe improvement of a variety of symptoms in gastroparesis and related disorders.

5.5 Refractory Patients with Gastroparesis

Patients with refractory gastroparesis need treatment at a variety of levels directed at nutritional care, prokinetic medications, antiemetic therapies, pain control, glycemic control, and often psychological measures. Surgical and endoscopic approaches are considered in patients in whom drug therapy is ineffective and who cannot meet their nutritional requirements (Camilleri et al. 1998). Surgical treatments include placement of jejunostomy tubes, gastric electrical stimulation, and pyloromyotomy (Camilleri et al. 1998). These options are typically considered only in patients with severe, refractory gastroparesis.

5.5.1 Psychotropic Medications as Symptom Modulators

Tricyclic antidepressants may have significant benefits in suppressing symptoms in some patients with nausea and vomiting as well as patients with abdominal pain. These are not used for their antidepressant effects, but their actions as symptom modulators, acting either peripherally or, most likely, centrally. Doses of tricyclic antidepressants used are lower than used to treat depression. A reasonable starting dose for a tricyclic drug is 10–25 mg at bedtime. If benefit is not observed in several weeks, doses are increased by 10–25 mg increments up to 50–100 mg. Side effects are common with the use of tricyclic antidepressants and can interfere with management and lead to a change in medication in 25% of patients. The secondary amines, nortriptyline and desipramine, may have fewer side effects. The recent NIH gastroparesis consortium study with nortriptyline in idiopathic gastroparesis did not show an effect on overall symptoms of gastroparesis (Parkman et al. 2013). However, there was a suggestion that low nortriptyline doses (10–25 mg) might decrease nausea, whereas higher doses (50–75 mg) might decrease fullness. There are limited data on the use of selective serotonin reuptake inhibitors in gastroparesis or functional dyspepsia.

5.5.2 Pyloric Botulinum Toxin Injection

Gastric emptying is a highly regulated process reflecting the integration of the propulsive forces of proximal fundic tone and distal antral contractions with the functional resistance provided by the pylorus. Manometric studies of patients with diabetic gastroparesis have shown in some patients prolonged periods of increased pyloric tone and phasic contractions, a phenomenon termed pylorospasm. Botulinum toxin is a potent inhibitor of acetylcholine neuromuscular transmission and has been used to treat spastic somatic muscle disorders as well as achalasia. Several studies have tested the effects of endoscopic injection of the pyloric sphincter with botulinum toxin in patients with diabetic and idiopathic gastroparesis (Camilleri et al. 1998). Initial studies were unblinded in small numbers of patients from single centers and have observed mild improvements in gastric emptying and modest reductions in symptoms for several months. Two double-blind studies have been reported; these show an improvement in gastric emptying, but no effect on symptoms compared to placebo. Thus, botulinum toxin injections do not result in sustained improvement in symptoms of gastroparesis.

5.5.3 Gastric Electric Stimulation

Gastric electric stimulation is a treatment for refractory gastroparesis. It involves an implantable neurostimulator that delivers a high-frequency (12 cpm), low-energy signal with short pulses. With this device, stimulating wires are sutured into the gastric muscle along the greater curvature during laparoscopy or laparotomy. These leads are attached to the electric stimulator, which is positioned in a subcutaneous abdominal pouch. Based on the initial studies that have shown symptom benefit especially in patients with diabetic gastroparesis, the gastric electric neurostimulator was granted humanitarian approval from the FDA for the treatment of chronic, refractory nausea and vomiting secondary to idiopathic or diabetic gastroparesis. The rare but worrisome complications of the implantable neurostimulator are infection of the pacemaker site and intestinal blockage from the intra-abdominal wires, which have necessitated device removal in approximately 5% of cases. More recently, a small minority of patients can at times have a shocking sensation. Symptoms of nausea and vomiting can improve with stimulation; however abdominal pain often does not. The symptomatic benefit occurs more often in diabetic gastroparesis than in idiopathic gastroparesis. In a recently reported cohort of 151 patients with refractory gastroparesis treated at a single center, GES improved symptoms in 75% of patients with 43% being at least moderately improved (Heckert et al. 2016). Response in diabetics was better than in nondiabetic patients. Nausea, loss of appetite, and early satiety responded the best.

Further investigation would be helpful to definitively show the effectiveness of gastric stimulation in long-term blinded fashion, which patients are likely to respond, the optimal electrode position, and the optimal stimulation parameters, none of which have been rigorously evaluated to date. Future improvements may include devices that sequentially stimulate the stomach in a peristaltic sequence to promote gastric emptying as well as endoscopically placed gastric electric stimulators.

5.5.4 Other Surgical Treatments for Persistently Refractory Gastroparesis Patients

Other treatments include feeding jejunostomy for nutritional support with a jejunostomy tube that bypasses the affected stomach for feedings. Venting gastrostomy tubes have been tried with success in some patients. Recently, pyloromyotomy has reemerged as a treatment for patients with gastroparesis. This can be performed surgically or more recently endoscopically. Open-label studies report good responses. Gastrojejunostomy has been performed in the past with limited success. Gastric bypass with gastrojejunostomy has been used by several centers to treat gastroparesis. Partial gastrectomy should be used rarely, and only in carefully selected patients. In postsurgical gastroparesis, occasionally completion gastrectomy is performed for persistent gastroparetic symptoms.

6 Concluding Remarks

Upper gastrointestinal function is complex with a variety of disturbances that may impact on symptom generation. Our understanding of the pathophysiology of upper gastrointestinal function in disorders is becoming better with newer modalities assessing motor function, accommodation, and sensation. The relationship of pathophysiology and symptom generation is also becoming better understood. The ability to study the various parameters of gastric function allows for better understanding of the relationships of upper digestive symptoms with alterations in gastric neuromuscular or CNS function. Treatment of upper gastrointestinal disorders is expanding and now often targets specific symptoms. In the future, it is plausible that clinicians will be able to employ selected tests chosen on the basis of clinical variables that will result in implementation of effective treatments leading to improved clinical outcomes.

Acknowledgment The author appreciated the discussions with Dr. Fernando Azpiroz.

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http://www.springer.com/978-3-319-56359-6

Gastrointestinal Pharmacology
Greenwood-Van Meerveld, B. (Ed.)
2017, VIII, 444 p. 100 illus., 30 illus. in color., Hardcover
ISBN: 978-3-319-56359-6