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REVIEW

Gastroparesis: a review of current and emerging treatment options

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Abstract: Gastroparesis is a motility disorder of the stomach causing delay in food emptying from the stomach without any evidence of mechanical obstruction. The majority of cases are idiopathic. Patients need to be diagnosed properly by formal testing, and the evaluation of the severity of the gastroparesis may assist in guiding therapy. Initially, dietary modifications are encouraged, which include frequent and small semisolid-based meals. Promotility medications, like erythromycin, and antiemetics, like prochlorperazine, are offered for symptom relief. In patients who are refractory to pharmacologic treatment, more invasive options, such as intrapyloric botulinum toxin injections, placement of a jejunostomy tube, or implantation of a gastric stimulator, can be considered. Hemin therapy and gastric electric stimulation are emerging treatment options that are still at different stages of research. Regenerative medicine and stem cell–based therapies also hold promise for gastroparesis in the near future.

Keywords: Gastroparesis, gastric emptying, gastric electrical stimulation, hemin

Introduction

Gastroparesis is a motility disorder of the stomach characterized by slowed emptying of food into the small bowel in the absence of mechanical obstruction.[1] Diagnosis is usually established by evaluation of the gastric transit time with scintigraphy (gastric emptying study using solids labeled with technetium). The exact incidence of gastroparesis is not known, but it is estimated to affect about 4%–5% of the population.[2] About 25%–55% of patients with insulin-dependent diabetes have diabetic gastroparesis, with a documented slightly higher incidence in patients with type 2 diabetes.[3–6] Patients with gastroparesis present with variable symptoms, but the most frequently encountered symptoms include nausea, vomiting, bloating, and abdominal pain.[7] Long-term gastroparesis is also associated with esophagitis, Mallory–Weiss tears, and severe peptic ulcer disease.[8]

Assessment of severity

The appropriate management of gastroparesis depends on the severity of the disease. There are multiple scoring systems available to access the severity of gastroparesis, but the two most commonly used systems are the Gastroparesis Cardinal Symptom Index (GCSI),[9] which is a validated scoring system, and the Abell's scoring system,[10] which has yet to be validated. The GCSI score is a sum of three subscale scores (each ranging from 1–3), for the three main symptom complexes:

- Postprandial fullness/early satiety
- Nausea/vomiting
- Bloating

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The Abell Scoring system grades the severity of gastroparesis as follows:[10]

- Grade 1 usually includes patients with mild intermittent symptoms that are controlled with diet modification and the avoidance of exacerbating agents.
- Grade 2 patients have moderately severe symptoms but no weight loss and require prokinetic drugs plus antiemetic agents for control.
- Grade 3 patients are refractory to medication, unable to maintain oral nutrition, and require frequent emergency room visits. These patients require intravenous fluids, medications, enteral or parenteral nutrition, and endoscopic or surgical therapy.

Treatment

General measures

Most patients with gastroparesis have dehydration and electrolyte disturbances on presentation. The objectives of treatment at this point include adequate hydration and correction of electrolyte imbalances, management of an underlying disorder (ie, diabetes mellitus), and alleviation of the presenting symptoms, such as nausea and vomiting, with medications. The patient's current medications should be reviewed, and those that may precipitate gastric dysmotility should be discontinued. Hyperglycemia has been shown to exacerbate the symptoms of gastroparesis, so blood glucose should be optimized appropriately.[11,12] Dietary modifications and symptom management with medications are recommended initially for patients with mild gastroparesis. Patients presenting with severe symptoms, such as pronounced dehydration or intractable vomiting, may need hospitalization, medications, or even more invasive interventions. These invasive interventions include intrapyloric botulinum toxin (BTX) (Botox®; Allergan Inc, Irvine, CA, USA) injections, placement of a feeding jejunostomy tube, or implantation of a gastric electrical stimulator. However, it must be mentioned that at this time, intrapyloric Botox injections and implantation of a gastric electrical stimulator remain controversial treatment options and offer varying results.

Dietary modifications

Dietary recommendations mainly involve adjustments to meal content and frequency. More liquid-based meals are recommended, as these patients usually have preserved gastric emptying with liquids. However, the intake of fats and nondigestible fibers should be discouraged as it is thought to worsen gastric emptying.[13,14] Smaller and less frequent meals have also been found to be very helpful.[15,16] Sometimes, patients may need enteral nutrition via a jejunostomy tube. Parenteral nutrition is usually reserved for patients who fail enteral feeding.[17]

Medications

Over the last decade, multiple research groups have been working towards the development of new medications that can improve gastric emptying and decrease the symptoms of gastroparesis. But no single agent has been proven to be effective in the management of gastroparesis, thereby making treatment of gastroparesis a challenging task for the health care provider.

Prokinetic medications

Prokinetic agents increase antral contractility, correct gastric dysrhythmias, and improve coordination between the antrum and duodenum, thereby promoting the movement of contents from the stomach.[17] These medications have modest efficacy, and their response should be judged clinically.[18]

Motilin receptor agonists

The macrolide, erythromycin is a potent prokinetic, but it has the side effects associated with being an antibiotic. However, the doses required for its gastric emptying effect are much lower than the doses associated with its antibiotic properties. The development of tolerance to the medication is a major problem.

Mitemcinal is a macrolide-derived motilin receptor agonist with prokinetic properties. Research has shown that a dose of 10 mg twice daily of mitemcinal had significant effects on upper gastrointestinal symptoms in patients with types 1 and 2 diabetes.[19]

Atilmotin, another motilin receptor agonist, when given intravenously, has been shown to accelerate gastric emptying of liquids and solids in healthy subjects, without significant effects on colonic transit.[20] No study has yet shown this effect on patients with gastroparesis.

Ghrelin is derived from the gastric mucosa and is similar in structure to motilin. It seems to play an important role in the regulation of appetite and body weight. Ghrelin has been shown to have prokinetic motility-stimulating properties in animals. It was also shown to accelerate gastric emptying after a test meal, in diabetic patients with slow gastric emptying,[21] while another study showed that the administration of ghrelin in patients with idiopathic gastroparesis improved gastric emptying.[22]

Dopamine receptor antagonists

Metoclopramide is currently the only US Food and Drug Administration (FDA)-approved medication used in the treatment of gastroparesis. It is a benzamide derivative that is structurally similar to procainamide. It primarily acts as a dopamine D2 receptor antagonist but stimulates 5-hydroxytryptamine 4 (5-HT4) receptors. These effects result in the release of acetylcholine within the gut wall, leading in turn to increased lower esophageal sphincter tone, antral contractility, fundic tone, and antroduodenal tone.[23] The resulting effect of accelerated gastric emptying has been demonstrated in several studies.[24,25] Metoclopramide can cross the blood–brain barrier, leading to multiple neurological changes. Discontinuation of the drug should be strongly considered once a suspicion of this side effect arises. Metoclopramide has also been shown to cause or precipitate extrapyramidal movement disorders, such as Parkinsonism, tardive dyskinesia, and akathisia. Somnolence, anxiety, depression, and reduced mental acuity have also been reported.[23,26,27]

Domperidone, another dopamine receptor antagonist, is only approved as an investigational drug in the United States. It chiefly acts as a peripheral dopamine D2 receptor antagonist, with a mechanism of action similar to that of metoclopramide. It accelerates gastric emptying by inhibiting fundic relaxation while promoting antroduodenal coordination and is presently widely used in many countries outside the United States.

Sulpiride is another dopamine antagonist that is currently used for some psychotic disorders. Itopride is a new D2 antagonist with antiacetylcholinesterase effects. Many studies have shown the prokinetic properties of itopride in animals but so far, similar results are lacking in human subjects.[28,29] One possible explanation for the effects of the D2 antagonists on gastrointestinal symptoms despite minimal effects on motility may be the action of these compounds on central emetic mechanisms.

5-HT4 agonists

Cisapride was formerly the treatment of choice for gastroparesis and gastroparesis-related symptoms. However, it has now been withdrawn from the market due to significant cardiac side effects. Presently, it is only available under compassionate care programs. No other 5-HT4 agonists have been approved for the treatment of gastroparesis.

The 5-HT4-agonist tegaserod has showed conflicting results in studies of gastric emptying in healthy subjects.[30,31]

Botulinum toxin

BTX has previously been used for the treatment of spasm in gastrointestinal sphincters, such as the lower esophageal sphincter, the sphincter of Oddi, and the anal sphincter. Recently, BTX has been injected intrapylorically for the treatment of gastroparesis. The BTX injections improve gastric emptying by decreasing the release of excitatory transmitter substances to the pyloric muscles. In recent research from Philadelphia on 63 patients with gastroparesis, 43% of the patients experienced a symptom response to BTX.[32] The duration of the response was approximately 5 months, and the response rate was higher in male patients compared with female patients. However, a crossover, randomized study from Belgium of 23 patients with predominantly idiopathic gastroparesis found that BTX was not superior to a placebo injection with respect to effects on symptoms and on gastric emptying.[33] The role of BTX remains controversial in the treatment of severe gastroparesis.

Gastric electrical stimulation

The frequency and direction of gastric peristalsis are determined by the gastric electrical slow wave rhythm. Many experiments in animals have shown that by increasing the electrical stimulation, the peristaltic pressure waves can be increased, resulting in improvement in nausea and vomiting.[34] These results have led to the development of a fully implantable electronic device.

Surgical interventions

Refractory gastroparesis, defined as the failure of symptoms to respond to medical therapy, coupled with the inability to meet nutritional requirements can be encountered in some patients. In these patients with severe gastroparesis, endoscopic and surgical options should be considered. Surgical placement of a jejunostomy tube should be considered in patients requiring frequent hospitalizations for hydration, nutrition, and medications. Laparoscopic jejunostomy can be performed safely. Some major complications, such as displacement, obstruction, and aspiration pneumonia, may result after the procedure.[35] In one retrospective study of patients with diabetic gastroparesis, 39% reported fewer symptoms of nausea and vomiting, 52% reported fewer hospitalizations, 56% reported better nutritional status, and 83% reported improved overall health after surgical intervention.[36] Simultaneous placement of a gastric tube with the laparoscopic jejunostomy may be necessary, to facilitate abdominal decompression and symptom relief. If laparoscopy is difficult or impossible to perform because of altered intra-abdominal

anatomy, the implantation can be performed by laparotomy. The latter technique prolongs postoperative hospital stay for most patients.[37]

Future directions

Advances in understanding the pathophysiology of gastroparesis have led to the development of many new potential treatment options and overall, the outlook is encouraging.[38] Induction of the heme oxygenase-1 pathway has been shown to counter cellular changes related to the gastrointestinal complications of diabetes. It is believed that high levels of heme oxygenase-1 exert a protective effect on the interstitial cells of Cajal by decreasing oxidative stress.[39] Currently, there is a pilot study going on that is investigating the efficacy of hemin, a therapy that induces heme oxygenase-1 expression in macrophages.[39] Further research is aimed at studying macrolide derivatives that are motilin receptor agonists that do not have antimicrobial activity. Gastric electrical stimulation has shown promising results in improving gastrointestinal symptoms. Regarding the goal of achieving sustainable stimulation, alternative options include long-pulse high-energy, single-channel, and multichannel with long pulse gastric electrical stimulation.[38] Other future treatment possibilities involve advances in regenerative medicine, particularly stem cell-based therapies. Stem cells are uncommitted cells characterized by their ability to undergo mitotic division and to cultivate into a variety of differentiated, specialized cells.[40] Upon reprogramming, these stem cells would theoretically be able to provide an unlimited source of patient-specific replacement cells.[40] Stem cell-based therapies would aim to restore tissue integrity, such as in the regeneration of interstitial cells of Cajal that are lost in diabetic gastroparesis or alleviation of the inflammatory changes seen in idiopathic gastroparesis.

Disclosure

The authors report no conflicts of interest in this work.

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