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REVIEW

Diabetic Gastroparesis: Therapeutic Options

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ABSTRACT

Gastroparesis is a condition characterized by delayed gastric emptying and the most common known underlying cause is diabetes mellitus. Symptoms include nausea, vomiting, abdominal fullness, and early satiety, which impact to varying degrees on the patient's quality of life. Symptoms and deficits do not necessarily relate to each other, hence despite significant abnormalities in gastric emptying, some individuals have only minimal symptoms and, conversely, severe symptoms do not always relate to measures of gastric emptying. Prokinetic agents such as metoclopramide, domperidone, and erythromycin enhance gastric motility and have remained the mainstay of treatment for several decades, despite unwanted side effects and numerous drug interactions. Mechanical therapies such as endoscopic pyloric botulinum toxin injection, gastric electrical stimulation, and gastrostomy or jejunostomy are used in intractable diabetic gastroparesis (DG), refractory to prokinetic therapies. Mitemcinal and TZP-101 are novel investigational motilin receptor and ghrelin agonists, respectively, and show promise in the treatment of DG. The aim of this review is to provide an update on prokinetic and mechanical therapies in the treatment of DG.

Keywords: diabetic gastroparesis; gastric electrical stimulation; ghrelin; mechanical therapy; prokinetic therapy

INTRODUCTION

Gastroparesis is characterized by a failure of normal gastric motility and emptying. The delay in gastric emptying leads to considerable morbidity due to nausea, vomiting, anorexia, and stomach fullness. Both type 1 and 2 diabetes mellitus are frequently associated with abnormal gastric motility,[1,2] and are a recognized cause of gastroparesis. The relationship between delayed gastric emptying and symptoms is variable, and individuals with delayed gastric emptying may be asymptomatic. Cross-sectional studies show that around 30%-50% of those with type 1 and 2 diabetes exhibit delayed gastric emptying.[3,4] Paradoxically, however, in the early stages of

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type 2 diabetes, there may be an accelerated phase of gastric emptying and enhanced proximal contraction resulting in nausea in individuals without overt neuropathy.[5,6] DG is a cause of significant morbidity in the form of recurrent nausea and vomiting in only a small minority of patients, whilst in others it may manifest simply as unpredictable hypo- and hyperglycemia with overall deranged glycemic control.[7] Thus, the phenomenon of "gastric hypoglycemia" is well documented[8,9] and may be an important cause of unexplained hypoglycemia in those who are classified as having brittle diabetes.[9]

MECHANISM OF GASTRIC EMPTYING AND THE PATHOGENESIS OF DG

Normal gastric emptying depends on synchronized tonic actions of the fundus and antrum with inhibition of pyloric and duodenal contractions.[10] Complex and highly integrated interactions occur between the gastric smooth muscle, myenteric plexus innervated by the vagal nerve, and gastric pacemaker cells (interstitial cells of Cajal [ICC]).[11] The primary defects leading to abnormal gastric emptying are vagal autonomic neuropathy and probable ICC pathology.[12,13] Neuropathy with subsequent aberrant postprandial response to hyperglycemia reduces the frequency of antral contractions and causes weak contractions of the proximal stomach. Glucose levels >140 mg/dL (~8 mmol/L) may diminish antral contractions and inhibit migratory motor complex (MMC) activity.[7] It is the lack of phase 3 of the MMC (during which ingestible solids are emptied into the duodenum) that leads to antral hypomotility in the fasting state, which ultimately leads to accumulation of large ingestible particles or bezoars. There is also excessive and prolonged tonic and phasic contractions of the pylorus, and this with the other mechanical abnormalities leads to delayed gastric emptying.

Dopamine is present in the gastrointestinal tract and inhibits gastrointestinal motility via the suppression of neuronal acetylcholine release by the D2 receptor.[14] This mechanism has been exploited therapeutically and forms the mainstay for therapeutic strategies using prokinetic agents. Additional alternative mechanisms include the direct effect of acute hyperglycemia causing a significant delay in gastric emptying,[15] by inducing motor dysfunction; therefore, improvement in glycemia can increase the rate of gastric emptying.[16] In both healthy subjects and patients with type 1 diabetes, acute changes in glycemia with a lowering of blood glucose has been shown to affect gastric motor function.[17,18] Even physiological hyperglycemia of 8 mmol/L in healthy subjects and patients with type 1 diabetes may prolong the gastric emptying time when compared with ~4 mmol/L. This suggests that glycemic control has a major role in gastric motor dysfunction.

Other factors that may play an important role in altering gastric emptying are hyperinsulinemia and insulin resistance, body mass index (BMI), smoking, and gender.[19-22] The phenomenon of nitric oxide "blunting" may lead to defects in gastric accommodation as evidenced by sildenafil accelerating gastric emptying in experimental studies[23] and indeed manifesting as an unwanted side effect of nausea in those taking phosphodiesterase type 5 (PDE5) inhibitors for erectile dysfunction. Abnormalities in glucagon homeostasis have also been implicated in the pathogenesis of DG.[24,25] Iatrogenic exacerbations of gastroparesis by therapies for hyperglycemia may be precipitated by agents that interfere with the neuroendocrine axis. Nausea may occur with metformin and this may well be related to the recently reported effect of metformin inhibiting dipeptidyl peptidase-4 (DPP-4) and raising glucagon-like peptide-1 (GLP-1).[26] Of course, both nausea and vomiting are common

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with GLP-1 analogs and are the most common causes of therapy failure.[24,25,27] Alternative diabetic agents that have also been implicated in exacerbating delayed gastric emptying are the amylinomimetic therapies such as pramlintide[28,29] (Table 1).

DIAGNOSIS

Although this review concentrates on medical and mechanical therapies, it is important to highlight routine standards of care when diagnosing DG. Other motility disorders can mimic DG, such as gastric outlet obstruction. Use of prokinetic therapy in the latter may significantly exacerbate symptoms and, therefore, it is important to exclude this disorder prior to initiating therapy. An esophagogastroduodenoscopy (EGD) or a barium meal should be performed prior to measurements of gastric emptying by scintigraphy, ^{13}C-acetate/^{13}C-octanoate breath test, or the SmartPill® device (SmartPill Inc., Buffalo, NY, USA). Other less commonly used methods include ultrasonography and electrogastrography (mainly for research).

Gastric emptying scintigraphy (GES) is considered the standard for measuring gastric emptying and there has been some progress towards using a single standardized protocol,[21,30] although this is currently not uniformly accepted. Historically, there have been inconsistencies in meal preparations, patient positioning, frequency, and duration of imaging, hence the normal range of values.[21] This posed problems in the interpretation and validation of the results, particularly from "outside" institutions. Limitations of other methods exist; breath tests assume normal small bowel and pulmonary function, the SmartPill is not widely available, and ultrasonography is operator dependent and generally only measures liquid emptying.[21] The suggested standardized test is by scintigraphy, using a low-fat, egg-white meal with imaging at baseline, 1, 2, and 4 hours after ingestion.[21]

MANAGEMENT

Key principles in the treatment of DG are the correction of exacerbating factors, which include regulation of glycemia, adequate nutritional support, and the use of prokinetic therapies, which have formed the cornerstone of treatment for DG.[31] The aim of treatment is to alleviate symptoms, shorten gastric emptying time, improve the nutritional status of the

Table 1. Diabetes therapies, the effects on gastric emptying, and mechanism of action.

Drug	Effect on gastric emptying and mechanism
Metformin	Possibly delayed: due to DPP-4 inhibition (gastric emptying studies required for definitive assessment)
Sulfonylureas	None
Glitazones	None
α-Glucosidase inhibitors (particularly arcabose)	Delayed: probably due to release of gut hormones including GLP-1 and CCK
Amylinomimetics	Delayed: inhibition of vagal cholinergic function
GLP-1 analogs	Delayed: inhibition of vagal cholinergic function and changes in neuroendocrine axis leading to reduced antroduodenal contractility
DPP-4 inhibitors	None: presumably because of lower GLP-1 concentrations than in GLP-1 analogs

CCK=cholecystokinin; DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1.

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patient, and thus optimize glycemic control. As previously discussed, hyperglycemia itself may delay gastric emptying and adequate control of glycemia is recognized as an important facet in the management of DG. However, there is little evidence to indicate that prokinetic agents may improve glycemic control through improved gastric emptying.[6]

PROKINETIC AGENTS

Prokinetic agents are the mainstay of treatment for DG and their use dates back to the 1970s.[32,33] However, there is a paucity of longitudinal studies demonstrating long-term effectiveness of prokinetic therapy. In part, this reflects the natural history of DG, which is often characterized by exacerbations and spontaneous remissions which do not require long-term therapy.

Metoclopramide

The use of metoclopramide has waxed and waned, particularly with the approval and subsequent withdrawal of cisapride.[14] Of the prokinetic agents, only metoclopramide has been licensed for use by the Food and Drug Administration (FDA) in DG. It is a potent central and peripheral dopamine-receptor (specifically D2 receptor) and to a lesser extent serotonin antagonist[34] acting on the brain stem and vagal nerves. It is thought to induce acetylcholine release from enteric neurons by antagonism of D2 receptors[14] increasing antral contractions.[35] Several clinical trials of metoclopramide have shown it to be an effective short-term therapy in DG,[32-35] although a longer duration of use may be associated with loss of gastrokinetic properties of the drug,[36] but there is a lack of longitudinal data confirming this. Randomized studies of metoclopramide have shown improvement in gastric emptying,[37-40] but this correlates poorly with symptoms.[39-40] This poor correlation of symptoms with functional deficits is typical of DG, especially as those with severe symptoms may only have mild-to-moderate impairment of gastric emptying.[41] Metoclopramide can cross the blood-brain barrier accounting for its significant central nervous system (CNS) side effects, which include anxiety, agitation, somnolence, insomnia, and movement disorders with long-term use, increasing the risk of developing intractable tardive dyskinesia (around 1%).[42] Hence surreptitious use of this medication is recommended and it is approved by the FDA for short-term (4-12 weeks) use only.[43] However, because DG is chronic, it is often prescribed indefinitely on an "as required" basis. Diabetes itself is a risk factor for tardive dyskinesia, along with female sex and younger age; the use of this drug,[14] further enhances the likelihood of CNS side effects in DG.

Domperidone

Domperidone is another dopamine (D2)-receptor antagonist that antagonizes peripheral receptors, particularly in the stomach, leading to enhanced stomach contraction.[11] It does not cross the blood-brain barrier and subsequently has a superior side-effect profile to metoclopramide with a lack of CNS effects.[44] Indeed, a study of metoclopramide versus domperidone by Patterson et al.[44] showed a significantly reduced CNS side-effect profile with domperidone, with greater tolerability but equal efficacy in improving symptoms. A number of studies over the past two decades have evaluated gastric emptying time, showing an improvement with the use of domperidone.[45-49] In the systematic review by Sugumar et al. in 2008,[49] 64% of studies showed significant efficacy for an improvement of symptoms, 60% showed an effect on gastric emptying, and 67% showed that domperidone effectively reduced hospital

admissions. However, the methodological content of the evaluated studies was poor with a lack of a placebo control group in most studies.[49] At present, domperidone is not FDA approved for gastroparesis, and obtaining the drug for clinical practice in the US requires an investigational new drug application to the FDA.[50] Dosing regimens and common side effects of dopamine (D2)-receptor antagonists are detailed in Table 2, along with other prokinetic agents.

Erythromycin and Motilin Receptor Agonists

Erythromycin is a motilin receptor agonist that is associated with increased antral contractions with improved gastric emptying,[51,52] particularly when administered intravenously.[52] Intravenous erythromycin is the drug of choice in relieving acute gastroparesis requiring hospitalization.[50-53] Dose tolerance may occur with chronic use,[51] and also due to the interactions with cytochrome P450 CYP3A4 inhibitors, it is not always a suitable therapy.[11] Other motilin agonists, such as azithromycin and clarithromycin, have been used but because they have not been extensively studied, they may be used only when gastroparesis symptoms are unresponsive to other prokinetics. Investigational motilin agonists, such as mitemcinal (GM-611) and ABT-229, lack the antibiotic activity of other drugs and have been assessed in clinical trials,[54-56] particularly as antibiotic resistance is considered to be of concern in chronic erythromycin use.[57] However, ABT-229 has failed to effectively control gastroparesis symptoms in placebo-controlled trials.[54,55] A study of mitemcinal showed a disparity between gastroparesis symptoms and gastric emptying, as the latter was enhanced without a significant difference in symptom relief between the active compound and placebo.[56] Mitemcinal may have a future role in the treatment of gastroparesis but requires further clinical trials to evaluate its safety and efficacy.

Table 2. Agents currently used in the treatment of diabetic gastroparesis.

Class of agent	Name(s)	Route (s)	Dosing	Side effects
Dopamine (D2)-receptor antagonists	Metoclopramide	PO, IV, SC, IM	10 mg TDS/ QDS before meals	Anxiety, depression, extrapyramidal movement disorders, galactorrhoea, tardive dyskinesia
	Domperidone	PO	10-20 mg TDS before meals	Side effects listed above plus: abdominal cramps, irregular menstrual periods, loss of libido
Motilin-receptor agonists	Erythromycin	PO, IV	40-250 mg TDS before meals	Abdominal cramping, early satiety, urticaria, rashes
	Clarithromycin	PO	125-250 mg OD	
	Azithromycin	PO	250 mg OD	
Acetylcholinesterase inhibitors	Pyridostigmine	PO	30 mg QDS	Sweating, bladder dysfunction, increased production of saliva, diaphoresis, muscle weakness

IM=intramuscular; IV=intravenous; OD=once daily; PO=oral; QDS=four times daily; SC=subcutaneous; TDS=three times daily.

Cisapride

Cisapride is a prokinetic agent that acts via 5-HT_4 receptors enhancing a cholinergic effect and inducing increased motor activity.[58] Previous studies comparing cisapride to other prokinetic agents have shown equivalent efficacy with both erythromycin and metoclopramide.[54,55] Indeed, gastric emptying is improved with cisapride administration;[59-63] however, due to safety concerns related to cardiac dysrhythmias, the drug was withdrawn from the USA[14] and, subsequently, the UK in 2000. Tegaserod, another 5-HT_4-receptor agonist used in DG, was again withdrawn due to cardiac safety concerns.

Ghrelin Agonists

Ghrelin is a recently discovered peptide that stimulates growth hormone release.[64-67] It is synthesized in endocrine cells in the gastric mucosa[61-63] and is believed to exert the majority of its actions through the receptor GHSR-1a,[68] which mediates gastric motility and emptying with the induction of MMC.[69] Ghrelin administration has been shown to enhance appetite and food intake[70,71] but other non-DG studies have shown no difference between ghrelin and placebo.[72] In a randomized, double-blind, crossover trial of ghrelin in DG by Murray et al.,[73] gastric emptying was increased but did not always favorably improve symptoms, a phenomenon also common to trials with other prokinetic agents.[54,56] Since the discovery of ghrelin, a number of molecularly similar receptor agonists have been used in clinical trials of gastrointestinal motility disorders.[74-76] TZP-101 is a selective intravenously administered agonist at the ghrelin receptor site. It appears to have a good safety profile in trials of healthy volunteers,[77] and has also been shown to be effective in enhancing gastric motility in DG[75,76] and accelerating recovery in surgical postoperative ileus.[74] Furthermore, an oral preparation (TZP-102) has been formulated, which is currently in phase 2 clinical trials. These novel ghrelin agonists show promise, particularly in view of the relatively poor side effect profiles of currently licensed prokinetic therapies.

Other Prokinetic Agents

Other agents include muscarinic agonists and anticholinesterases such as bethanechol and pyridostigmine, respectively, and may be used in DG, but data assessing effects on gastric emptying are lacking.[50]

MECHANICAL THERAPIES

A number of nonpharmacological treatments have been used with varying success in the management of DG.

Acupuncture

The underlying mechanism of acupuncture in reducing symptoms of gastroparesis is unknown.[10] Efficacy has been reported for symptoms in a single-blind, randomized trial of electroacupuncture.[78] Dyspeptic symptoms were reduced and solid gastric emptying was accelerated. Further studies are required to investigate the possible benefits of acupuncture in DG.

Botulinum Toxin

Pylorospasm (excessive, prolonged contractions of the pylorus) is recognized as a manifestation of DG and has been investigated with antroduodenal manometry.[79,80] Botulinum toxin is an inhibitor of neuromuscular

transmission at cholinergic terminals,[81] and has been used in achalasia.[82] Whilst several uncontrolled studies have suggested efficacy,[83] two previous placebo-controlled trials have not shown superiority of botulinum toxin over placebo in managing DG.[84,85] Neither study had antroduodenal manometry, particularly considering that small intestine motor dysfunction can range anywhere from 17% to 85% in DG.[83] Botulinum toxin may still be an effective therapy particularly in those with pylorospasm; however, routine use is not recommended at present.

Gastric Pacing

Recently, gastric electrical stimulation therapy (gastric pacing) has been approved by the FDA (Enterra therapy, Medtronic, Minneapolis, MN, USA).[4] The National Institute for Health and Clinical Excellence (NICE) advises that gastric electrical stimulation is an option for the treatment of patients with chronic, intractable, drug-refractory nausea and vomiting.[86] Although patients suitable for this procedure are relatively uncommon, those with severe symptoms may well benefit.[86] Gastric electrical stimulation delivers impulses at high frequency/low energy (short pulses) at around 12 pulses per minute via a pacemaker. The device is implanted on the anterior abdominal wall and leads are implanted in the serosa of the greater curvature of the stomach. Both the severity and frequency of symptoms improved in open-label studies, which were maintained for up to 4 years.[87-91] The underlying basis for improved symptoms has again not been consistently related to accelerated gastric emptying.[88] Central effects and increases in postprandial gastric accommodation have been suggested, but the precise mechanism remains uncertain. Infection is the major complication of this treatment, requiring removal of the device in approximately 10% of patients.

Surgical Therapies

Surgical treatments may be used in those with severe intractable DG who are often hospitalized on multiple occasions. Gastrostomy may be used to alleviate severe symptoms such as nausea, vomiting, and bloating,[92] although persistent symptoms may still exist despite surgery due to small bowel denervation and dysmotility.[93] Jejunostomies are indicated to maintain fluid balance and nutritional status,[92] and can be an effective "last resort" measure.[92] Interestingly, pancreatic transplantation has been shown to benefit those with DG.[94] Studies assessing neuropathy have shown early nerve fiber regeneration in type 1 diabetic patients after pancreas transplantation,[95] and this may be the potential basis for relieving symptoms, but of course, overall improved glycemic control must play a role in improving gastric emptying.

CONCLUSION

The rising prevalence of diabetes will inevitably result in increasing rates of chronic complications including gastroparesis. Patients develop a variety of symptoms that do not always correlate with the degree of abnormality on gastric emptying. Current treatment options are limited; however, novel investigational agents of the motilin and ghrelin class show promise. Intractable DG may require intervention with gastric electrical stimulation or surgery.

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