Gastroparesis: Optimizing Management and Improving Outcomes

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Gastroparesis

Definition: A chronic symptomatic disorder of the stomach characterized by delayed gastric emptying in absence of mechanical obstruction.

Symptoms:
- nausea, vomiting,
- early satiety, postprandial fullness, abdominal distension,
- upper abdominal pain.

Diagnosis:
- Symptoms
- Upper endoscopy
- Gastric emptying test
Causes of Gastroparesis

Three main causes
  Diabetic
  Postsurgical
    Past: Vagotomy, resection for ulcers
    Present: Nissen fundoplication, Bariatric surgery
  Idiopathic
    Postviral in some

Other causes
  Metabolic Disorders: Hypothyroidism
  Generalized GI Motility Disorder: Intestinal pseudo-obstruction
  Medications: narcotics, anticholinergics

Clinical Characteristics of Patients with Gastroparesis
(146 Patients at Tertiary Motility Centers)

<table>
<thead>
<tr>
<th>Gender:</th>
<th>Female 82%</th>
<th>Male 18%</th>
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</thead>
<tbody>
<tr>
<td>Age at onset of Symptoms:</td>
<td>34 years</td>
<td></td>
</tr>
<tr>
<td>Symptoms:</td>
<td>Nausea 92%</td>
<td>Vomiting 84%</td>
</tr>
</tbody>
</table>

Causes of Gastroparesis:
  Diabetic 29%
  Postsurgical 14%
  Idiopathic 28%
  Postviral 8%

Parkinson’s 10%
Pseudoobstruction 4%
Scleroderma 4%

McCallum et al. 1998
**Trends of Gastroparesis-Related Hospitalizations**

_United States, 1995-2004_

![](image)

Hospitalizations:
- Gastroparesis as primary diagnosis increased +158%.
- Gastroparesis as secondary diagnosis increased +136%.
- Diabetes-related increased +53%.
- All hospitalizations increased +13%.

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**Gastric Emptying: Regional Gastric Function**

Gastric emptying reflects coordinated function of the fundus, corpus, antrum, pylorus, duodenum:
- Fundic relaxation and accommodation
- Antral contractions for triturating/grinding
- Pyloric sphincter opening for final emptying

Wang, Fisher, Parkman. AJG 2008
Techniques to Evaluate Gastric Emptying

Scintigraphy:
- Standard test
- Variable methodology clinically
- Standardization of Meal and Imaging

Wireless Motility Capsule:
- Office Based Test, easily standardized
- Gastric emptying / contractility
- Empties with resumption of phase III
- Measures Whole Gut Transit

GE Breath Test:
- Office Based Tests, easily standardized
- Presently used in Europe clinically
- Used in US in research studies

Symptoms and Delayed Gastric Emptying

Symptoms of gastroparesis are not well correlated with gastric emptying.

Symptoms associated with delayed gastric emptying in patients with functional dyspepsia (idiopathic gastroparesis) are primarily postprandial fullness, nausea and vomiting.

In patients with diabetes, symptoms associated with delayed gastric emptying are abdominal bloating/fullness and upper abdominal pain.

In patients undergoing gastric emptying test, only nausea, vomiting, and early satiety were associated with delayed gastric emptying.

1499 patients undergoing GES (21.3% diabetics, 9.5% prior gastric surgery), 629 (42%) had increased retention at 4 hrs (>10%). The symptoms correlating with gastric retention at 4 hours included early satiety, vomiting, feeling excessively full after meals, and loss of appetite.
**General Principles for Treatment of Gastroparesis**

Correction of fluid, electrolyte, nutritional deficiencies

Identification and treatment of the underlying cause

Suppression or elimination of symptoms, primarily N/V

Quigley, Hasler, Parkman. Gastroenterology 2000; 120:263

**Therapeutic Approach to Gastroparesis**

Dietary manipulations

Strive for euglycemia in the diabetic patient

Prokinetic therapy

Antiemetic therapy

?Analgesic therapy
Dietary/Nutritional Treatment for Gastroparesis

Diet modifications
- Low roughage, low fat, low fiber
- Small meals

More frequent meals (3 meals with 2 snacks)

Change from solid food to primarily liquid meals

Oral Nutrient Supplementation

Jejunostomy feeding tube for long-term

TPN, generally not recommended

Current Status of Prokinetic Agents

Metoclopramide (Reglan)
- FDA-approved agent for gastroparesis (12 w for DG
- Prokinetic and antiemetic
- CNS side effects in 10-20%

Domperidone (Motilium)
- Not to be released in USA.
- FDA IND/IRB
- Prokinetic and antiemetic
- Side effects: low lactation, prolong QTc

Erythromycin
- GI side effects - N/V/Abd pain
- Tachyphylaxis to effect
- ?Cardiac effects

Being studied:
- 5HT-4 receptor agonists
- Motilin receptor agonists
- Ghrelin receptor agonists
**Metoclopramide for Diabetic Gastroparesis**

Randomized, double-blind, controlled trial of metoclopramide in 10 patients with diabetic gastroparesis

- Metoclopramide increased gastric emptying
- Overall symptoms and symptoms of vomiting were reduced during metoclopramide treatment.
- Poor correlation between improved gastric emptying and decreased symptoms.

**Metoclopramide improves symptoms of diabetic gastroparesis:**
- Peripheral effect of gastric smooth muscle to increase gastric emptying
- Central effect on chemoreceptor vomiting zone to decrease nausea.


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**A Double-blind Multicenter Comparison of Domperidone and Metoclopramide in the Treatment of Diabetic Patients with Symptoms of Gastroparesis**

93 type 1 diabetic patients with gastroparesis symptoms were treated with either domperidone 20 mg po QID or metoclopramide 10 mg po QID for 4 weeks.

- Domperidone and metoclopramide were equally effective in alleviating symptoms of diabetic gastroparesis.

- Adverse CNS effects were more severe and more common with metoclopramide than with domperidone:
  - Somnolence, reduction in mental acuity.

Patterson, Abell, Rothstein, Koch, Barnett. Am J Gastro 1999;94:1230
Domperidone in the Management of Symptoms of Diabetic Gastroparesis

Single-Masked Study: 208/269 (77%) patients with diabetic gastroparesis improved on Domperidone 20 mg po QID
Randomized Placebo-Controlled, Double-Masked Withdrawal Phase: Placebo group had greater deterioration in total symptom scores compared to domperidone

Erythromycin in the Short-Term and Long-Term Control of Dyspepsia Symptoms in Gastroparesis

25 patients with gastroparesis
Treated with low dose erythromycin suspension (50-100 mg TID)
Randomized, Placebo-Controlled Trial of Botulinum Toxin A for the Treatment of Delayed Gastric Emptying

32 patients randomized to receive either Botox 200 units in 5 ml (n=16) or Saline 5 ml (n=16) into the pylorus

Friedenberg, Palit, Parkman, Nelson. Am J Gastroenterology 2008

Antiemetic Agents for Gastroparesis

<table>
<thead>
<tr>
<th>Class of Agent</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prokinetic agents with antiemetic properties (antagonize dopamine receptors)</td>
<td>Metoclopramide (Reglan)</td>
</tr>
<tr>
<td>Phenothiazine derivatives (antagonize dopamine receptors in area postrema)</td>
<td>Prochlorperazine (Compazine)</td>
</tr>
<tr>
<td>Anticholinergic agents</td>
<td>Scopolamine patch</td>
</tr>
<tr>
<td>Antihistamines (H₁ receptor antagonists)</td>
<td>Diphenhydramine (Benadryl)</td>
</tr>
<tr>
<td>Antiserotonergic (5-HT₃ receptor antagonists)</td>
<td>Ondansetron (Zofran)</td>
</tr>
<tr>
<td>Substance P/Neurokinin-1 Receptor Antagonists</td>
<td>Aprepitant (Emend)</td>
</tr>
</tbody>
</table>
Other Forms of Antiemetic Rx for Refractory Patients

- Low dose Tricyclic Antidepressants
- Marinol
- Relief Band
- Jejunostomy feeding tube
- Venting gastrostomy tube
- Gastric electrical stimulation

Tricyclic Antidepressants for Chronic Vomiting in Diabetic Patients

24 diabetic patients treated with tricyclic antidepressants for nausea and vomiting after an unsatisfactory response to prokinetic therapy.
TCAs: Amitriptyline, nortriptyline, desipramine.
Starting doses 10-25 mg/day; final maintenance dose: 10-75 mg/day.

Sawhney, Prakash Lustman, Clouse. DDS 2007;52:418.
Nortriptyline for Idiopathic Gastroparesis

Gastric Electric Stimulation (Enterra) Therapy

High frequency, low energy, short pulse duration stimulation; not gastric pacing.

FDA Humanitarian Device Exemption (HDE) for treatment of chronic, intractable (drug refractory) nausea & vomiting secondary to diabetic or idiopathic gastroparesis.

Mechanism of action not elucidated:
  Increase gastric emptying
  Enhance fundic relaxation (accommodation)
  Decrease gastric sensitivity
  Affect afferent sensory pathways to central mechanisms for N/V

Effect of GES Based on GP Subtype and Main Symptom

Maranki, Parkman et al. DDS 2010
Laparoscopic pyloroplasty for gastroparesis results in sustained symptom improvement

Retrospective review of prospectively collected data of 28 patients who underwent minimally invasive pyloroplasty alone as treatment for gastroparesis from Jan 2007 to Sept 2010.

A laparoscopic Heineke-Mikulicz pyloroplasty was performed in 26 of 28 patients.

GES T1/2 decreased from 320 to 112 min.

Improvements were seen at 1 month for nausea, vomiting, bloating, abdominal pain, and GERD symptoms.

Improvement persisted at 3 months for nausea, vomiting, bloating, abdominal pain and GERD symptoms.

Minimally invasive pyloroplasty provides excellent outcomes for patients with gastroparesis.


Management of Gastroparesis

Symptoms Suggestive of Gastroparesis
(Nausea, Vomiting, Early Satiety, Fullness)

Establish the Diagnosis of Gastroparesis
Upper endoscopy or Upper GI Series
Rule out other organic etiologies
  e.g. ulcer disease, mechanical obstruction

Gastric Emptying Test
(GES with 4-hour EggBeats Meal)
Alternative Scintpill or Breath Test

Delayed GE

Initial Treatments
  Dietary modifications
  Prokinetic (Metoclopramide)
  Antiemetic (Compazine) pm or RTU
  Glucose control

No Improvement

Other Treatment Trials
  Other Prokinetic Agents: Erythromycin
  Domperidone
  Other Antiemetic Agents: Ondansetron

No Improvement

Consider Further Treatment Options
  Symptom Mediator (TCA)
  Botulinum Toxin Injection
  Feeding Jejunostomy
  Gastric Electrical Stimulation
Diabetic Gastroparesis

Associated with long-standing Insulin-Dependent Diabetes (T1DM).

Seen in T2DM (NIDDM), where rapid gastric emptying can occur early in the disease.

Frequently occurs with other diabetic complications

neuropathy, retinopathy, nephropathy (“triopathy”)

Gastroparesis is analogous to neuropathy of vagus nerve

May cause difficulty with glycemic control: hypoglycemia

NB; Hyperglycemia also delays gastric emptying
Treatment Approach to Gastroparesis

Multiple Areas to Address

Hydration and Nutrition

Dietary Changes

Prokinetic Treatment

Antiemetic Treatment

Glucose Control in Diabetic Patients

Pain Control

Psychological

Treatment of Gastroparesis

General Items
Avoid medications that can delay stomach emptying
Glucose control for diabetic patients

Diet
low fiber and roughage
low in fat (fat increases CCK and delays GE)
Liquid nutrients are better tolerated over solid food
small meals, usually multiple 4-6/day
Nutrition Consultation

Antiemetic Agents
Compazine, Tigan (affect CNS vomiting center)
Ondansetron, a 5-HT-3 receptor antagonist

Reduce N/V

Prokinetic Agents
Metoclopramide, a dopamine receptor antagonist
Erythromycin, a motilin receptor agonist
Domperidone, a dopamine receptor antagonist

Speed gastric emptying
## Prokinetic Medication Classes

<table>
<thead>
<tr>
<th>Class of Agent</th>
<th>Available</th>
<th>Special Circumstances</th>
<th>Under Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine antagonists</td>
<td>Metoclopramide</td>
<td>Domperidone</td>
<td>Itopride</td>
</tr>
<tr>
<td>Motilin agonists</td>
<td>Erythromycin</td>
<td>?Clarithromycin</td>
<td>Mitemcinal</td>
</tr>
<tr>
<td>Ghrelin agonists</td>
<td>Ulimorelin</td>
<td>TZP-102</td>
<td></td>
</tr>
<tr>
<td>5-HT3 agonists</td>
<td>Cisapride</td>
<td>Tegaserod</td>
<td>Renzapride</td>
</tr>
<tr>
<td>Muscarinic agonists</td>
<td>Bethanechol</td>
<td></td>
<td>AT1-7505</td>
</tr>
<tr>
<td>Acetylcholinesterase inhibitors</td>
<td>Physostigmine</td>
<td>Neostigmine</td>
<td>YM443 (Z-338)</td>
</tr>
<tr>
<td>CCK receptor antagonists</td>
<td></td>
<td></td>
<td>Loxiglumide</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Dexloxiaglumide</td>
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## Antiemetic Medication Classes

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<tr>
<th>Class</th>
<th>Examples</th>
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<tbody>
<tr>
<td>Dopamine D2 antagonists</td>
<td>Metoclopramide, Domperidone</td>
</tr>
<tr>
<td>With prokinetic activity</td>
<td></td>
</tr>
<tr>
<td>Without prokinetic activity</td>
<td><strong>Prochlorperazine</strong>, Trimethobenzamide</td>
</tr>
<tr>
<td>Serotonin 5-HT3 antagonists</td>
<td><strong>Ondansetron</strong>, Granisetron,</td>
</tr>
<tr>
<td></td>
<td>Dolasetron, Tropisetron</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td><strong>Desipramine</strong>, Nortriptyline,</td>
</tr>
<tr>
<td></td>
<td>Amitriptyline</td>
</tr>
<tr>
<td>Muscarinic M1 antagonists</td>
<td>Scopolamine, Hyoscyamine</td>
</tr>
<tr>
<td>Histamine H1 antagonists</td>
<td>Dimenhydrinate, Meclizine, <strong>Promethazine</strong></td>
</tr>
<tr>
<td>Cannabinoids</td>
<td><strong>Marinol</strong>, Tetrahydrocannabinol</td>
</tr>
<tr>
<td>Benzdiazepines</td>
<td>Lorazepam</td>
</tr>
<tr>
<td>Neurokinin NK1 antagonists</td>
<td>Aprepitant</td>
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Initiation of Enteral Nutrition
Surgical Jejunostomy

Severe weight loss
(weight loss > 10% of usual body weight over 6 months)

Repeated hospitalizations for refractory gastroparesis intravenous hydration and/or intravenous medication.

Better absorption of medications to gain therapeutic levels when vomiting prevents this.

Gastric decompression: Gastrostomy/jejunostomy tube(s).

Gastric electrical stimulation improves symptoms from diabetic gastroparesis in a prospective study.

Enterra gastric electrical stimulation uses an implantable neurostimulator with a high-frequency, low-energy output.

A controlled, multicenter, prospective study to evaluate the safety and efficacy of Enterra therapy in patients with chronic intractable nausea and vomiting from diabetic gastroparesis (DGP).

Patients with refractory DGP (n = 55; mean age, 38 y; 66% female, 5.9 years of DGP) underwent treatment with Enterra gastric stimulation. After surgery, all patients had the stimulator turned on for 6 weeks and then they randomly were assigned to groups that had consecutive 3-month, cross-over periods with the device on or off. After this period, the device was turned on in all patients and they were followed up, unblinded, for 4.5 months.

In patients with intractable DGP, 6 weeks of initial GES therapy with Enterra reduced vomiting and gastroparetic symptoms. The double blind cross over portion over 3 months was not significant. Patients had improvements in subjective and objective parameters with chronic stimulation after 12 months of GES, compared with baseline.

Predictive Factors for Clinical Improvement with Enterra Gastric Electric Stimulation Treatment for Refractory Gastroparesis

The Temple Experience (2004-2006)

Overall, 14 of 28 (50%) patients felt improved.
- GCSI decreased by 12±7% from 3.3±0.2 to 2.7±0.2.
- Nausea/vomiting subscore improved by 30±7%.
- Abdominal pain did not change.

Three Predictive Factors for Symptom Improvement:
- Diabetic patients improved better than idiopathic patients
- Patients with chief complaint of nausea/vomiting did better abdominal pain.
- Patients taking regular narcotic analgesics at the time of implant had a poorer response compared to those not taking narcotics.

Gastroelectric Stimulation (Enterra) Therapy

Enterra Therapy is indicated for the treatment of patients with chronic, intractable (drug refractory) nausea and vomiting secondary to gastroparesis of diabetic or idiopathic etiology.

FDA Statement on Enterra - Humanitarian Device Exemption (HDE) of a Humanitarian Use Device (HUD)

Still need medical insurance approval. Often initially denied – experimental.

Devised to improve gastric emptying.
Response does not depend on improving gastric emptying.
Other proposed mechanisms – fundic relaxation, afferent stimulation to central nausea/vomiting control mechanisms.