Diabetic Gastroparesis

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Background

- Gastroparesis is a syndrome characterized by delayed gastric emptying, in the absence of mechanical obstruction of the stomach.
- The cardinal symptoms include postprandial fullness, nausea, vomiting, and bloating.
- Diabetes mellitus (DM) is responsible for almost one third of cases of gastroparesis.
Background

- Gastroparesis typically develops after at least 10 years of evolution of DM, and often is associated with other complications.
- It may cause severe symptoms and result in nutritional compromise, impaired glucose control, and a poor quality of life, independently of other factors.
- Symptoms connected to gastroparesis are reported by 5 to 12% of DM.
Symptoms

- Nausea
- Retching
- Vomiting
- Stomach fullness
- Not able to finish a normally sized meal
- Feeling full after meals
- Loss of appetite
- Bloating
Diagnostic Testing

- Barium X-ray
- Upper endoscopy
- Scintigraphy: food labeled with 99m technetium; gamma rays emitted from the radionuclide are captured as counts by a camera; serial images quantify the counts that remain in the stomach
- Breath testing: $^{13}\text{C}$ isotope can be incorporated into a solid meal; once absorbed and metabolized by the liver, $^{13}\text{CO}_2$ is excreted in the lungs and can be measured.
- Smart pill
- Ultrasound for measuring gastric emptying
- Gastric manometry
Mild gastroparesis is characterized by symptoms that are easily controlled. Moderate gastroparesis is associated with moderately/severe symptoms, partially controlled with medications; nutrition is maintained with the use of dietary and lifestyle changes, and treatment in the hospital is rarely required. Severe gastroparesis with gastric failure: symptoms are refractory despite medical therapy, nutrition cannot be maintained through the oral route, and emergency room visits or hospitalizations are required.
Management

- **Key principles:**
  1. the correction of exacerbating factors, including optimization of glucose and electrolyte levels;
  2. nutritional support
  3. the use of prokinetic and symptomatic therapies.

- **Areas to address:**
  1. Hydration and nutrition
  2. Dietary changes
  3. Prokinetic drugs
  4. Antiemetic treatment
  5. Glucose control
  6. Pain control
  7. Psychological
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mild (10–15%)</th>
<th>Moderate (16–35%)</th>
<th>Severe (&gt;35%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consumption of homogenized food</td>
<td>When symptomatic</td>
<td>When symptomatic</td>
<td>Routinely, and use of liquid nutrient supplements</td>
</tr>
<tr>
<td>Nutritional supplementation</td>
<td>Rarely needed</td>
<td>Caloric liquids by mouth or, rarely, by PEJ tube</td>
<td>PEJ tube may be required</td>
</tr>
<tr>
<td>Pharmacologic treatment</td>
<td>Metoclopramide (Reglan), 10 mg as required, and dimenhydrinate (Dramamine), 50 mg as required</td>
<td>Metoclopramide, 10 mg thrice daily before meals by mouth, or domperidone (Motilium), 10–20 mg thrice daily before meals, with or without erythromycin (e.g., E-mycin), 40–250 mg thrice daily before meals, and dimenhydrinate, 50 mg as required, or prochlorperazine (Compazine), 25 mg as required</td>
<td>Metoclopramide, 10 mg thrice daily before meals by mouth, or domperidone, 10–20 mg thrice daily before meals, with or without tegaserod (Zelnorm), 2–6 mg twice daily, or erythromycin, 40–250 mg thrice daily before meals, and dimenhydrinate, 50 mg as required, prochlorperazine, 25 mg as required, or intravenous 5-HT₃–receptor antagonist (e.g., ondansetron [Zofran])</td>
</tr>
<tr>
<td>Nonpharmacologic treatment</td>
<td>Not needed</td>
<td>Not needed</td>
<td>Gastrostomy-tube decompression and PEJ feeding, parenteral nutrition, or compassionate use of gastric electrical stimulation</td>
</tr>
</tbody>
</table>

* The severity of gastroparesis, types of drugs listed, and recommendations for nutritional support are based on guidelines of the American Motility Society and the American Gastroenterological Association. The priorities for treatments in each category are based on clinical experience. In general, management progresses from the top down, according to the patient’s response to treatment. PEJ denotes percutaneous endoscopic jejunostomy.

† Typical gastric retention of solid food at 4 hours correlates with the severity of gastroparesis and provides some guidance on selection of treatment but should not be used alone to guide treatment.
Pharmacological agents

- Prokinetic agents
- Antiemetic agents
- Pain control
<table>
<thead>
<tr>
<th>Agent</th>
<th>Primary mode(s) of action</th>
<th>Proposed physiological effects (foregut)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopaminergic Metoclopramide</td>
<td>Dopamine-2-receptor antagonist</td>
<td>Antiemetic effect</td>
</tr>
<tr>
<td></td>
<td>Serotonin type 4 (5-HT₄)-receptor agonist</td>
<td>Accelerates gastric emptying</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreases visceral sensitivity</td>
</tr>
<tr>
<td>Domperidone</td>
<td>Dopamine-2-receptor antagonist</td>
<td>Antiemetic effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Accelerates gastric emptying</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increases gastric antral motility</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreases visceral sensitivity</td>
</tr>
<tr>
<td>Itopride</td>
<td>Dopamine-2-receptor antagonist</td>
<td>Antiemetic effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Accelerates gastric emptying</td>
</tr>
<tr>
<td></td>
<td>Cholinesterase inhibitor</td>
<td>Antiemetic effects</td>
</tr>
<tr>
<td>Levosulpiride</td>
<td>Dopamine-2-receptor antagonist</td>
<td>Accelerated gastric emptying</td>
</tr>
<tr>
<td></td>
<td>Serotonin type 4 (5-HT₄)-receptor agonist</td>
<td>Decreases visceral sensitivity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increases gastric antral motility</td>
</tr>
<tr>
<td>Motilin</td>
<td>Motilin receptor agonist</td>
<td>Antiemetic effect</td>
</tr>
<tr>
<td>Erythromycin</td>
<td></td>
<td>Accelerates gastric emptying</td>
</tr>
<tr>
<td>ABT229</td>
<td></td>
<td>Reduces gastric fundic accommodation</td>
</tr>
<tr>
<td>Serotonergic Mosapride</td>
<td>Serotonin type 4 (5-HT₄)-receptor agonist</td>
<td>Antiemetic effect</td>
</tr>
<tr>
<td></td>
<td>Serotonin type 3 (5-HT₃)-receptor antagonist</td>
<td>Accelerated gastric emptying</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increases gastric antral motility</td>
</tr>
<tr>
<td>Tegaserod</td>
<td>Partial serotonin type 4 (5-HT₄) -receptor agonist</td>
<td>Antiemetic effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Accelerates gastric emptying</td>
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Source: Aliment Pharmacol Ther © 2006 Blackwell Publishing
Commonly used agents

**Metoclopramide**

- i.v. in severe cases
- if chronic, adverse effects in up to 30%
  - hyperprolactinemia: gynecomastia, breast tenderness, galactorrhea, amenorrhea
  - 10% CNS effects: restless, insomnia, drowsy
  - 1% extra-pyramidal reactions
- ! risk of tardive dyskinesia (women, elderly, >12 weeks therapy)
**Erythromycin**

- stimulates both fasting and feeding antral contractions
- side effects: abdominal cramps, diarrhea are common
- only 30% able to tolerate, acute side effects, tachyphylaxis
Domperidone

- Symptom improvement correlates better with resolution of gastric dysrhythmia than with normalization of emptying rates.
- Better tolerated: adverse effects in less than 7%, no CNS side effects.
Other agents

- **Cisapride** is associated with an increased risk of cardiac arrhythmia; not available since 2000.
- Muscarinic cholinergic agents (e.g., **bethanechol**) increases amplitude of contractions, not a true prokinetic agent.
- The 5-hydroxytryptamine4 (5-HT4) agonist **tegaserod** may accelerate gastric emptying, but data from trials assessing effects on symptoms of gastroparesis are lacking. Used in IBS, withdrawn since 2007.
- **Mosapride**: gastroprokinetic agent
- **Itopride**: dual effect, not yet approved in US and GB
- **Levosulpiride**: antipsychotic, antiemetic and prokinetic
- **Sumatriptane** (serotonin agonist) improves meal-induced satiety in patients with functional dyspepsia
- **Buspirone** has anxiolytic, but also fundic relaxant properties
- **Clonidine** has been reported to decrease symptoms and accelerate gastric emptying in diabetic patients with gastroparesis, although others have observed slowing of emptying with the drug.
Anti-emetic agents

- Dopamine D2 antagonists with prokinetic activity (Metoclopramide, Domperidone)
- Dopamine D2 antagonists without prokinetic activity (Prochlorperazine)
- Serotonin 5-HT3 antagonists (Ondansetron)
- Tricyclic antidepressants (Desipramine, Amitriptyline)
- Muscarinic M1 antagonists
- Histamine H1 antagonists
- Cannabinoids (Marinol)
- Benzodiazepines (Lorazepam)
Non-pharmacological methods

- **Botox injections into pylorus**: Botulinum toxin type A binds to presinaptic acetylcholine terminals and produces blockade at the level of the neuromuscular junction, preventing cholinergic transmission and promoting muscle relaxation.

- **Gastric electric stimulation (Enterra) therapy**: for chronic, drug refractory nausea and vomiting secondary to diabetic/idiopathic gastroparesis. High frequency, low energy, short pulse duration stimulation; mechanism of action not fully elucidated (increase gastric emptying, decrease gastric sensitivity, enhance fundic relaxation).
Take home points

- Diet and lifestyle changes, prokinetics and anti-nausea medications are the mainstay of therapy
- The current therapy available is suboptimal, so,
- Novel medications and devices are currently being studied and offer promise
Thank you!

“I don’t feel good. That twelfth piece of fudge I ate must have been bad.”