Gastroparesis: Are We Moving On?

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Disclosures

- Consultant – Alkermes, Allergan, Forest, Ironwood, Prometheus, Salix

- I will be discussing off-label uses of domperidone and tricyclic anti-depressants for the treatment of gastroparesis.

Objectives

- Review clinical definition, functional anatomy, symptoms and causes of gastroparesis

- Outline a practical approach to the diagnosis of gastroparesis

- Review currently available treatment options

Gastroparesis: Clinical Overview

*Gastroparesis literally means gastric ‘paralysis’*

Can only be ‘diagnosed’ with a gastric emptying test

Presenting symptoms are non-specific:
- epigastric pain/discomfort
- nausea/vomiting/regurgitation
- bloating/early satiety
- weight loss/failure to thrive

Most common in diabetics, young women & post gastric surgery

Anatomic and Functional Motor Regions of the Stomach

- Anatomic
  - Body (corpus)
  - Fundus
  - Pylorus

- Functional motor
  - Antrum pump
    - Phasic contractions
  - Gastric reservoir
    - Tonic contractions

Pacemaker potentials determine contractile parameters
**Neurohumoral Control of Gastric Motility**

- Stomach: Gastric contraction - Head: Gastric 
  - Intragastric pressure (cm H2O)
  - Barostat volume (ml)
  - Lipid (2 kcal/ml) Solutions infused into the duodenum at a rate of 1 ml/min
  - NaCl (0.9%) Intragastric pressure
  - 15 12 9 6 3 0
  - Lipid + CCK A Antagonist
  - Barostat volume (ml)

**Interstitial Cells of Cajal are Decreased in Gastroparesis**

ICC are the pacemakers of the GI tract and transmit neuronal signaling to the smooth muscles. ICC are depleted in up to 50% of patients with either idiopathic or DM gastroparesis.

- **Normal**
- **Gastroparesis**

**Diabetic Gastroparesis**

- Autonomic neuropathy
- Loss of ICC has been the main finding; other findings include:
  - altered immune function such as type 2 macrophages
  - loss NO synthase in enteric neurons
  - smooth muscle atrophy
- Serum glucose > 250 mg/dL is associated with delayed emptying
- Impaired receptive relaxation
- Hypersensitivity

**Common Causes of Gastroparesis**

- Idiopathic: 40-50%
- Diabetes: 30-40%
- post-surgical: 10-20%

**Medications that Reduce Gastric Emptying**

- Opiates
- Anticholinergics
- Tricyclic antidepressants
- Calcium channel blockers
- Lithium
- Nicotine
- Clonidine
- Progesterone
- GLP-1 analogs (e.g. exenatide, liraglutide, dulaglutide)
Disorders to Consider in the Differential Diagnosis

- Rumination syndrome and/or eating disorders (e.g., anorexia nervosa and bulimia)
- Cyclic vomiting syndrome (CVS) defined as recurrent episodic episodes of nausea and vomiting
- Chronic usage of cannabinoid agents. Patients presenting with symptoms of gastroparesis should be advised to stop using these agents.

Diagnosis of Gastroparesis

- Exclude mechanical causes (PUD, Gastric cancer, proximal bowel obstruction) with EGD, UGI with SBFT, and/or cross-sectional imaging
- Gastric emptying (discontinue medications that delay GE x 48º and glucose < 200):
  - 4 hour scintigraphy: most reliable. Shorter studies result in decreased sensitivity
  - Breath testing (i.e., spirulina 13 C breath testing)
  - Wireless Motility Capsule

Gastric Scintigraphy

![Gastric Scintigraphy Diagram]

Management of Gastroparesis: The Essentials

Diet:
- frequent small nutrient meals, low in fat and soluble fiber
- if unable to tolerate solids, then homogenized or liquid food
- if oral intake is insufficient, then jejunostomy tube feeding should be pursued (after a trial of N tube feeding)
- Consider enteral nutrition when: unintentional loss of >10% of usual body weight during a period of 3–6 months, and/or repeated hospitalizations for refractory symptoms
- Enteral feeding is preferable to TPN

Diabetics: optimize glycemic control; avoid pramlintide the injectable amylin analogue and GLP-1 analogs
Pharmacological Treatments Options

- Prokinetics
  - D2 antagonist (metoclopramide, domperidone)
  - Motilin Agonist (erythromycin)

- Anti-emetics
  - 5HT3 Antagonist (ondansetron, dolasetron, granisetron)
  - Phenothiazines (Compazine, phenergan)
  - Cannabinoids (dronabinol)
  - Benzodiazepines (lorazepam)

Gastroparesis: Prokinetics

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<thead>
<tr>
<th>DRUG CLASS</th>
<th>MECHANISM</th>
<th>NOTES</th>
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<tbody>
<tr>
<td>D2 antagonist</td>
<td>Antiemetic &amp; proaccomodation effects via serotonin receptors</td>
<td>Best at improving symptoms. Tardive dyskinesia AEs in 30%</td>
</tr>
<tr>
<td>Peripheral D2 antagonist</td>
<td>Antiemetic &amp; proaccomodation effects via serotonin receptors</td>
<td>Limited CNS issues Hyperprolactinemia Concerns regarding QT prolongation</td>
</tr>
<tr>
<td>Motilin receptor agonist</td>
<td>Improves interprandial digestion</td>
<td>IV &gt; po Low dose reduces AEs and tachyphylaxis</td>
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* Not approved by the FDA. Available with an IND

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Metoclopramide

- Only FDA approved prokinetic
  - 5-10 mg TID: may be administered po, ODT, IM, IV, SQ
  - Should be administered at the lowest effective dose in a liquid formation to facilitate absorption.
  - The risk of tardive dyskinesia < 1 %. Patients should be instructed to discontinue therapy if they develop side effects including involuntary movements. (Box warning)
  - Caution in use in the elderly and prolonged therapy (>12 weeks)
  - Other AEs: restless, drowsiness, galactorrhea, akathisia

Domperidone

- Peripherally selective D2 receptor antagonist
- Increases prolactin and therefore sometimes used to increase lactation
- Associated with QT prolongation via hERG channel blockade. Risk appears to be dose-dependent
- Not approved by the FDA though may be obtained with an IND through the FDA

Erythromycin

Motilin Receptor Agonist

- Stimulates both antral contractions and augments phase III MMC
- AEs: abdominal cramps, diarrhea

Other Potential Motilin Agonists

- Azithromycin
- Semi-Synthetic non-peptide motilin agonists
  - PF-04548043
  - Mitemcinal
- Synthetic non-peptide agonist
  - GSK962040
- Motilin peptide Analog
  - Atilmotin
Ghrelin: Gastroparesis

- Tack et al. studied 6 pts (5 women) with idiopathic gastroparesis.
- Ghrelin increased liquid emptying, trended to increase solid emptying, and improved symptoms of fullness and pain.
- Murray et al. - DM gastroparesis saline vs. ghrelin infusion
  - Increase in GER in 7/10. No change in symptoms with ghrelin

Gastroparesis: Antiemetics

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<tr>
<td>Antihistamines</td>
<td>Non-selective H1 receptor antagonists that crosses the blood brain barrier</td>
<td>1st generation antihistamines Sedation is common</td>
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<tr>
<td>Phenothiazines</td>
<td>D2 receptor antagonist vomiting center of brain</td>
<td>AEs include dystonia, pseudoparkinsonism, and akathisia</td>
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<td>5-HT3 Antagonists</td>
<td>Black peripheral sensation of gastric distension</td>
<td>No prokinetic effects</td>
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<tr>
<td>NK1 antagonist</td>
<td>Approved for post-chemo vomiting</td>
<td>APRON study: 46% aprepitant vs 40% placebo, P=0.63; met primary endpoint</td>
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<tr>
<td>Cannabinoids</td>
<td>Good for anticipatory nausea</td>
<td>THC stimulates appetite</td>
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Nortriptyline Does Not Improve Symptoms of Idiopathic Gastroparesis: The NORIG Randomized Clinical Trial

Nortriptyline dose was increased at 3-week intervals (10, 25, 50, 75 mg) up to 75 mg at 12 weeks. These findings do not support the use of nortriptyline for idiopathic gastroparesis.

Relamorelin, a Grelin Agonist, Improves Diabetic Gastroparesis Symptoms in Patients with Vomiting

- Abdominal Pain
- Nausea
- Early satiety

Beyond Medical Therapies...

- Pyloric botulism toxin
- Neuroenteric gastric stimulator
- Feeding tubes: gastrostomy vs jejunostomy
- Pyloric myotomy (surgery, POEM)
Neuroenteric Gastric Stimulation

![Impact of Gastric Stimulation Therapy on Vomiting](image)

Gastroparesis: Conclusions

- Symptoms associated with gastroparesis are nonspecific and therefore require further evaluation.
- Gastric emptying assessment is necessary to diagnose gastroparesis.
- Treatment options include dietary modifications, prokinetics, anti-emetic and visceral analgesics.
- The efficacy of neuroenteric stimulation, pyloric botox injection or myotomy have not definitively established.