Gastroparesis

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Agenda:

• ACG practice Guidelines 2013
• Symptoms, Definitions, Epidemiology
• Pathophysiology
• Treatments Paradigms
Gastroparesis: Definition

Symptoms and delayed gastric emptying in the absence of a fixed mechanical obstruction of the pylorus or small intestine or ulceration.

Diabetic Gastropathy

- Symptom complex with functional, contractile, electrical and sensory dysfunction of the stomach associated with diabetes
- Pain, rapid emptying, delayed emptying
Gastroparesis: suggestive symptoms

• Early satiety/anorexia/food avoidance
• Bloating/fullness
• Heartburn
• Nausea/Vomiting
• Abdominal pain
• Weight loss
  • Relationship to meals

Gastroparesis vs Functional Dyspepsia

• Symptoms Identical!
• Difference in gastric emptying delay
  – Is slight delay practically normal?
  – Slight delayed gastroparesis = functional Dyspepsia
    • Epigastric Pain Syndrome, Postprandial Distress Syndrome

• IBS-C versus Constipation
  – Primary complaint
    • Pain vs Nausea vs Early Satiation
Gastroparesis: Causes

- **Mechanical**: outlet obstruction from cancer or PUD, HPS
- **Metabolic and endocrine**: DKA, diabetic*, hypothyroid, electrolyte imbalance
- **Post-gastric surgery***: vagotomy, partial gastrectomy, obesity surgery, Roux en Y
- **Acid-peptic disease**
- **Gastritis**: atrophic, pernicious anemia, acute viral gastroenteritis
- **Collagen vascular disease**: scleroderma
- **Medications**: anticholinergics, narcotics, levodopa, salbutamol, loperamide, GLP-1 and amylin analogues
- **Pseudo-obstruction**: idiopathic, secondary (amyloidosis, MD, paraneoplastic)
- **Electrical dysrhythmia**: tachy, brady, or gastroduodenal dysynchrony
- **Central nervous system mediated**: tumor, bulbar poliomyelitis, depression
- **Idiopathic***
- **Prodrome (Viral)**

Pathophysiology of gastroparesis

1. Fundal hypomotility
2. Antral hypomotility
3. Antpyloroduodenal segment “spasm”
4. Gastric pacemaker dysrhythmias
5. Excessive inhibitory feedback

Adapted from Brian Lacey
Factors that slow gastric emptying

- size
- density
- lipids
- acidity
- tonicity

Gastroparesis: Evaluation

- History - timing of nausea/vomiting relative to meals
  - immediately, s/p 30 min, several hours later
  - Predominant symptom: N/V, early satiation, pain?
- glucose, electrolytes, acid-base, thyroid, HCG, drug levels, ANA
- EGD
- UGI-SBFT: r/o outlet obstruction and inflammation, small bowel lesion, assess SB transit time
- Measure of Gastroduodenal Motility Function
  - Gastric emptying test, gastroduodenal manometry
Gastric Scintigraphy

- radiolabeled meal still the “common standard”
- widely available, well tolerated
- allow solid- and liquid-phase studies
- assess global stomach neuromuscular activity
- wide normal range
- radiation exposure
- takes 2-4 hours

Gastric emptying scans: Advantages

- Widely available but not always 4 hrs
- Solid phase scans should be performed for 4 hours
- Solid phase scans are the most sensitive for detecting gastroparesis
- Results are reported as the % of the meal retained (or emptied) after a specific time period
- Gastroparesis defined as mean +/- 2 SD
- Consider rapid emptying
Gastric emptying scans: Disadvantages

- Poor correlation between symptoms and emptying times
- Large variability within individual patients
- Results influenced by gender, serum glucose, weight, and menstrual cycle
- Results from short studies (90 mins) are extrapolated and are usually incorrect
- Poor standardization between sites
- Results do not predict response to therapy

Wireless Motility Capsule: Measure of Gastric Function

- Capsule that measures pH, pressure, temp
- Measures Gut Transit and Motility
  - Gastric and small bowel transit time
  - Antral and prox small bowel contractility
- Ambulatory Test
  - Capsule swallowed with test meal
  - Emptying of an Indigestible Object by MMC
- Normal Gastric Emptying Time (<5 hrs)
- Correlation with scintigraphy of .80 at 4hrs
FIGURE 1. Prevalence of physiologic abnormalities calculated by GES, GET, as well as gastric and proximal small bowel pressure measurements (PM) by WMC.

Gastric Emptying Tests (Others)

- Gastric Bezoar or retained food during EGD after overnight fast
- Breath tests $^{13}$C-octanoic acid, platensis, etc
  - indirect measure, noninvasive, reproducible, no radiation (stable isotope)
  - need normal intestinal absorption, liver metabolism, and lung function
  - FDA approved, No CPT
- MRI
  - measure rate of emptying and contractility
  - time-consuming, expensive, research

Current Treatment of Gastroparesis

- Correct underlying condition
  - Review medications! control hyperglycemia!
- Hydration and nutrition
- Dietary changes
  - small frequent meals, less residue, low fat
- Medical treatment
- Behavioral Modification/Psychiatric Treatment
- For failures, decompression (PEG) and nutrition (PEJ) only after trial of NG and NJ tubes
Medications that Slow Gastric Emptying

- anticholinergic agents
- antidepressants
- beta-adrenergic agonists
- calcium channel blockers
- ganglion blocking agents
- levodopa
- nicotine
- octreotide
- opiates
- tranquilizers
- vincristine

Treatment of Gastroparesis – Dietary Recommendations

- Small frequent meals - 5 to 6 per day
- Low fat
- Low fiber
- Emphasize liquids (bouillon, Gatorade)
- Supplement diet with egg whites, protein powders, and nutritional drinks (Enlive, low fat Ensure)
- Control serum glucose
Three-step Dietary Treatment

STEP 1: rehydration Day 1-2
    - sip Gatorade or salty bouillon solution to ingest goal 1-1.5L over 24 hours, multiple vitamin
    - avoid citrus or highly sweetened drinks

STEP 2: diet advance to soups
    - soups with noodles/rice and crackers, 6 small-volume meals per day, goal 1500 cal/day and maintain/gain weight
    - avoid fatty foods

STEP 3: introduction of more solid foods
    - starches (require less electrocontractile work), white meat
    - avoid red meat, fresh vegetables, fiber

Nutritional Status

- Hypo and hyperglycemia impact gastric emptying
- Low residue diets, low fiber
  - Gastric bezoars
- TPN- temporary or permanent option
  - Complications and logistical issues
- Enteral Feeding
  - Venting G tubes- may modulate accommodation
  - Feeding J tubes
Prokinetic Therapies

- Metoclopramide
- Erythromycin
- (Domperidone)
- (Cisapride)

Metoclopramide

- A substituted benzamide derivative
  - Chemical structure similar to procainamide
- Available since 1979
- Increases ACh release from intrinsic neurons
- Inhibits DA receptors centrally and peripherally
- Increases the tone and amplitude of antral contractions
- Relaxes the pyloric sphincter
- FDA approved for diabetic GP
Metoclopramide: Side Effects & Tardive Dyskinesia

- 30-40% of patients have side effects
  - Anxiety, depression, insomnia, “skin crawling”, acute dystonic reaction, akathisia, Parkinsonism
- 37 cases of NMS; 8 deaths
- New black box warning (FDA – 2-26-09)
- TD - an extrapyramidal disorder characterized by irreversible involuntary movements
- Some reports state risk is as high as 15%
- FDA: chronic use should be avoided

Metoclopramide & Tardive Dyskinesia

- Likely an idiosyncratic reaction
- Real risk: < 1%
- In UK – 16 million dose; 4 cases of TD
- In Scandinavia – risk estimated at 1 every 2000-2800 treatment years
- Risk factors: age > 70; women; length of use (>20 months); and higher doses (32 mg/day)
- Recommendation: Discuss with patients; use cautiously, use lowest effective dose
Domperidone

- A benzamidazole derivative
- Acts peripherally to block D2 receptors
- Increases local release of ACh
- Antiemetic activity is due to DA receptor blockade in the CTZ
- Side effects due to elevated prolactin levels
- PO form only; IV form may lead to arrhythmias

Domperidone: Gastroparesis

- 11 studies performed to date in Pts with GP
  - 4 = open label; 1 single-blind
  - Subjects: 3 to 287
  - Doses: 10 mg TID to 20 mg QID
  - Study length: 4 weeks to 2 years
  - Outcomes: Symptoms and/or gastric emptying
  - Results: Symptoms improved in 36% - 94%
  - Gastric emptying improved in 0 – 64%
  - Similar or better than metoclopramide
Cisapride

- facilitate ACh release and directly stimulate smooth muscle
- no dopaminergic activity
- improve gastroduodenal coordination
- side effects rare: cramping, diarrhea
- cardiac arrhythmias noted esp. with macrolides or antifungals possibly via HERG channels: withdrawn from market by FDA

Erythromycin

- A macrolide antibiotic
- Mimics the action of motilin
- Induces Phase III of the MMC
- Increases the amplitude of antral contractions and increases antro-duodenal coordination
- Ideal dose is 1-2 mg/kg per dose
- FDA approved for diabetic GP
- Tachyphylaxis is common & expected
Summary: Prokinetic agents

- Few large well-controlled trials
- Few long-term studies
- Poor correlation between symptoms and effects on gastric emptying
- Symptoms may be improved compared to placebo\(^1\)
  - cisapride = 8%
  - metoclopramide = 36%

\(^1\) Sturm, Digestion 1999; 60: 422

Antiemetic Therapies

- Phenothiazines (compazine)
- Antihistamines (meclizine)
- Anticholinergics (scopolamine)
- DA antagonists (metoclopramide)
- 5HT-3 antagonists (ondansetron)
- Others: marinol, lorazepam, prednisone, haldol

- Delay gastric emptying
Abd Pain in Gastroparesis

- Is as prevalent as Nausea, vomiting, early satiation
- Variable intensity
- Challenge with Narcotics and TCAs (anticholinergic)
- Tramadol- very weak opioid with serotonin/Norepinephrine effects
- Gabapentinoids- less effect on GI motility
- Need to define symptom priority
  - Pain or N/V/early satiation
  - Cyclic vomiting syndrome

Nortriptyline on symptoms of idiopathic gastroparesis

- 15-week multicenter, parallel-group, placebo-controlled, double-masked, randomized clinical trial
  - NIDDK Gastroparesis Clinical Research Consortium (GpCRC) for symptomatic relief in idiopathic gastroparesis
  - Delays gastric emptying and moderate to severe symptom scores using the Gastroparesis Cardinal Symptom Index (GCSI)
  - Nortriptyline vs placebo.
  - Study drug dose was increased at 3-week intervals (10, 25, 50, 75 mg) up to 75 mg at 12 weeks.

- **MAIN OUTCOMES AND MEASURES:**
  - primary outcome measure of symptomatic improvement
  - decrease from the patient's baseline GCSI score of at least 50% on 2 consecutive 3-week GCSI assessments during 15 weeks of treatment.

- **RESULTS:**
  - The primary symptomatic improvement outcome did not differ between 65 patients randomized to nortriptyline vs 65 patients randomized to placebo
  - 19 (23% [95% CI, 14%-35%]) in the nortriptyline group vs 14 (21% [95% CI, 12%-34%]) in the placebo group (P = .86).
  - Treatment was stopped more often in the nortriptyline group (19 [29% {95% CI, 19%-42%}] vs 6 [9% {95% CI, 3%-19%}] (P = .007).
  - Adverse events were not different (27 [95% CI, 18-39] vs 28 [95% CI, 19-40]) (P = .89).

- **CONCLUSIONS AND RELEVANCE:**
  - With idiopathic gastroparesis, use of nortriptyline compared with placebo for 15 weeks did not result in improvement in overall symptoms.

Parkman et al. JAMA. 2013
**Botox & Gastroparesis:**  
A Systematic Review

- 15 trials to date
  - only 2 were R, PC trials
- Arts (2007; Europe) – 100 U Botox; 4 week FU
  - 23 Patients: 19 idiopathic; 2 DM; 2 post-op
  - no change in symptoms using GCSI or GES
- Friedenberg (2008; USA) – 200 U Botox; 4 week FU
  - 32 Pts: 18 DM, 13 idiopathic; 1 post-op;
  - no change in symptoms using GCSI or GES

**Surgery and gastroparesis**

- G tube Venting?
- Only role is for placement of J tubes for enteral nutrition after trial of tube feeding
- Would like to confirm function of small bowel
  - SBFT transit time
  - Wireless Motility capsule- transit time, prox small bowel contractility
  - Antroduodenal manometry
- Failure of TPN feeding or SB function
  - TPN with inherent complications
    - Line sepsis

*Courtesy of Brian Lacy*
Gastric Stimulation

- Electrodes are implanted laparoscopically on the serosa, during open surgery, endoscopically
- Electrical stimulation occurs at a frequency faster than the intrinsic slow wave of the stomach
- Current delivered is low (5 mA), and duration varies (300 millisec to 300 microsec)

Gastric Stimulation: MOA

- Theoretically, entrainment (pacing) of gastric slow waves can be achieved with low frequency/long duration pulses.
- Not Increase gastric emptying.
- ? Vagal nerve stimulation with modulation of CTZ and nausea and vomiting center.
  - Very appealing
  - PET study – GES increases activity in thalamus
  - But, why does it work in some patients who have had a vagotomy?
Gastric stimulation

- 14 studies published to date; only 1 = blinded
- 6 different publication groups total
- Study size: 5-214 (most = 18-33)
- Most are mixed groups (DM and idiopathic)

Gastric Stimulation

- Bottom line:
  - Improves nausea and vomiting in 50% of Pts
  - 76% of Pts were able to stop TPN/PPN
  - Some improvement in glycemic control
  - Not helpful for pain or bloating
  - Less helpful for those on narcotics
  - Not improve GES
  - Not change gastric electrical rhythm
  - Better in diabetics than non-diabetics
  - Appears to improve Patients’ quality-of-life
Future Drugs

- other 5HT$_4$ agents: serotonergic agonists
- opioid receptor modifiers
- Cisapride-like compounds
- Motilin agonists
  - No anti-biotic properties, ? tachyphylaxis
- Ghrelin agonists
  - Phase II trials for diabetic gastroparesis

Behavioral Therapy and Psychopharmacology

- Pain component, fear of eating
- Psychosocial factors which exacerbate symptoms
  - control and manipulation behavior
- Cognitive Behavioral Therapy
  - coping strategies and stress relaxation techniques
- Antidepressants
  - avoid anticholinergic activity
  - desiprimine and trazadone
  - SSRIs: fluoxetine, citalopram
Potential Non-Drug Treatments

- Acupuncture point P6 (Neiguan point) - reduction of nausea (Koch, K.L. et al. 1997)
  - postoperative nausea and vomiting (Dundee, J.W., et al., 1989)
  - cancer chemotherapy (Dundee, J.W., et al., 1991)

Complex Management- Careful Combos

- Nausea/vomiting
  - Anti-emetic
  - Visceral hypersensitivity
- Early satiation
  - Pro-motility
- Pain
  - Visceral Hypersensitivity