Gastroparesis Update Highlights: Dr. McCallum's Clinical Research and Experience

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What is Gastroparesis?

- Gastroparesis, is defined as delayed gastric emptying with associated symptoms in the absence of any evidence of mechanical obstruction of the stomach or the upper GI tract.
- Gastroparesis is a functional gastrointestinal motility disorder meaning there is an abnormality in nerve, muscle and/or electrical activity in the stomach.
- The cardinal symptoms are early satiety, postprandial fullness, nausea, bloating, upper abdominal pain, GE Reflux, and with more severe illness, vomiting - >1 hr. after meals - usually 2-6 hours.
- In advanced cases there is weight loss, malnutrition, dehydration, electrolyte imbalance, hypo/hyper-glycemic fluctuations, bezoar formation and aspiration pneumonia.
- It affects up to 4% of the population in the United States, with 70% female; median age: 50 years.
Etiologies of Idiopathic Gastroparesis (IG)

- Post Infectious

**Entities Mimicking IG**
- Connective Tissue Disorder
- Hypermobility Syndrome
- Ehlers-Danlos / Pots Syndrome
- Median Arcuate Ligament Syndrome
- CNS Degenerative Diseases
- Paraneoplastic Syndrome
- Functional (Non-ulcer) Dyspepsia
- Miscellaneous

**Medication Induced**
- Opioids
- THC Derivatives
- Diabetic Medications
Approximately, 40% of patients refractory to medical therapy and requiring surgical intervention have depletion of ICC in the antrum or gastric body.

C-Kit Staining of antral smooth muscle for ICC

Normal (>10 ICC/HPF)  Gastroparesis

ICC LOSS IN THE ANTRUM CORRELATES WITH DYSREGULATED GASTRIC SLOW WAVES AND DECREASED GASTRIC EMPTYING

Depleted ICC: <10/HPF
Normal ICC: ≥10/HPF

Location of EGG Electrodes

Lin & McCallum, Neurogastroenterol Motil. 2010 Jan;22(1):56-6
MOLECULAR THEORY UNDERLYING GASTROPARESIS:
DIABETIC AND IDIOPATHIC GASTROPARESIS IS ASSOCIATED WITH LOSS OF CD206-POSITIVE MACROPHAGES IN THE GASTRIC ANTRUM

An M2 to M1 shift in gastroparesis is linked with the loss of ICC and nNOS neurons.

TREATMENT OF GASTROPARESIS

- Restoration of hydration, electrolytes and nutrition
  - Liquid soft diet, low fat – low fiber
  - Caloric liquid supplements
- Treat nausea – antiemetics
- Restore coordinated gastric and small bowel motility with prokinetic agents
- Glycemic control
- Pain control
- Psychological measures
- Botulinium toxin pyloric injections
- Feeding tubes – endoscopic or oral
- Surgery
  A) Jejunal feeding tube, full thickness gastric biopsy
  B) Placement of gastric electrical stimulation (GES) system
  C) Pyloroplasty
  D) Gastric surgery- gastric bypass in obese diabetics (BMI > 40) with gastroparesis
MEDICAL MANAGEMENT OF GASTROPARESIS

**Standard of treatment includes:**

<table>
<thead>
<tr>
<th>Antiemetics</th>
<th>Prokinetics</th>
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<tr>
<td>Compazine (Prochlorperazine)</td>
<td>Erythromycin Phenergan®</td>
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<tr>
<td>(Promethazine)</td>
<td>Reglan® (Metoclopramide)/Gimoti- Nasal Spray</td>
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<tr>
<td>Zofran® (Ondansentron)</td>
<td>Motilium® (Domperidone)</td>
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<td>Emend (Aprepitant)</td>
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<td>Scopolamine patch</td>
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<td>Marinol</td>
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- Brain-Gut modifiers: TCA (Amitriptyline, Nortriptyline) & Remeron (Metarzapine)
RECOMMENDATION REGARDING INITIATING REGLAN THERAPY FROM MEDICO-LEGAL STANDPOINT

- Discuss with patient, available family members & with a nurse present all the side effects expected with Reglan.
  - a) Emphasize initial first day namely “muscle spasm” type immediate reactions (1-5% range)
  - b) The early onset side effects (within first week) namely anxiety – akinesia, insomnia or excessive sleep and fatigue (20% range)
  - c) Long term side effects namely depression, Parkinsonism, prolactin related & rare tardive dyskinesia (1-5% range)

*Overall side effects could be in to excess of 30%*

- Document all this discussion in the office chart and medical record or in a specifically designed informed consent which patient and/or nurse also sign.
Multicenter Domperidone Trial: Significant Reduction in Symptom Scores in Phase I

![Graph showing symptom scores](image)

- Abdominal Pain: Baseline 2.03, Week 4 0.74
- Nausea: Baseline 2.33, Week 4 0.78
- Bloating/Distention: Baseline 2.55, Week 4 1.06
- Early Satiety: Baseline 2.43, Week 4 0.98
- Vomiting: Baseline 0.97, Week 4 0.23

*P<0.001

Data on file, Janssen Pharmaceutica Inc.
NEW DATA ON DOMPERIDONE

• New Evidence that High Dose Domperidone (>40 mg a day)- range of 80-120 mg/ day has cardiac safety and good clinical efficacy
CONCLUSIONS FROM ERYTHROMYCIN LITERATURE

- Erythromycin has strong gastric prokinetic effect
  - Both Intravenous and oral routes effective

- Small bowel motility enhanced but not small bowel transit

- Initiate low oral dosing of 250 mg 3 times per day – may increase dose but limited by side effects and concerns for tachyphylaxis

- Useful if other prokinetics have side effects or not effective and in combination with antiemetic agents
BACKGROUND & AIMS:

There are few effective treatments for nausea and other symptoms in patients with gastroparesis and related syndromes. We performed a randomized trial of the ability of the neurokinin-1 receptor antagonist aprepitant to reduce symptoms in patients with chronic nausea and vomiting caused by gastroparesis or gastroparesis-like syndrome.

METHODS:

We conducted a 4-week multicenter, double-masked trial of 126 patients with at least moderate symptoms of chronic nausea and vomiting of presumed gastric origin for a minimum of 6 months. Patients were randomly assigned to groups given oral aprepitant (125 mg/day, n = 63) or placebo (n = 63). The primary outcome from the intention-to-treat analysis was reduction in nausea, defined as a decrease of 25 mm or more, or absolute level below 25 mm, on a daily patient-reported 0-100 visual analog scale (VAS) of nausea severity. We calculated relative risks of nausea improvement using stratified Cochran-Mantel-Haenszel analysis.

RESULTS:

Aprepitant did not reduce symptoms of nausea, based on the primary outcome measure (46% reduction in the VAS score in the aprepitant group vs 40% reduction in the placebo group; relative risk, 1.2; 95% CI, 0.8-1.7) (P = .43). However, patients in the aprepitant group had significant changes in secondary outcomes such as reduction in symptom severity (measured by the 0-5 Gastroparesis Clinical Symptom Index) for nausea (1.8 vs 1.0; P = .005), vomiting (1.6 vs 0.5; P = .001), and overall symptoms (1.3 vs 0.7; P = .001). Adverse events, predominantly mild or moderate in severity grade, were more common in aprepitant (22 of 63 patients, 35% vs 11 of 63, 17% in the placebo group) (P = .04).

CONCLUSIONS:

In a randomized trial of patients with chronic nausea and vomiting caused by gastroparesis or gastroparesis-like syndrome, aprepitant did not reduce the severity of nausea when reduction in VAS score was used as the primary outcome. However, aprepitant had varying effects on secondary outcomes of symptom improvement. These findings support the need to identify appropriate patient outcomes for trials of therapies for gastroparesis, including potential additional trials for aprepitant. ClinicalTrials.gov no: NCT01149369.
Future gastroparesis pipeline:

A) Antiemetics: Tradipitant- VANDA (beyond Aprepitant; antagonist of human substance P/neurokinin 1 (NK1)- phase 3 trials in progress.

B) Prokinetic agents:
   1) Ghrelin agonists: Relamorelin- Rhythm Pharma, phase 3
   2) 5HT-4 agonists: Velusetrag- Theravance Pharma, phase 3
   Prucalopride-Shire-now Takeda Pharma
   3) Dopamine 2 and 3 antagonists:
      a) intranasal metoclopramide- Evoke Pharma, phase 3
      b) Domperidone-like agents with no cardiac toxicity: TAK-906 (ATC-1906): in phase 2 trials
      c) Neurogastrix- agent from Europe, to be studied in USA
TRICYCLICS FOR NAUSEA AND VOMITING

- Main experience with Amitriptyline and Nortriptyline with median dose 50 mg/d (range 25-200mg)
- Successful in patients unresponsive to prokinetics and with delayed gastric emptying (Prakash, Clouse et al. Dig Dis Sci, 1998)
- Additional ameliorating effects on epigastric/abdominal pain often present in gastroparesis patients
- NIH Gastroparesis Consortium Study: Limited efficacy in idiopathic gastroparesis (JAMA 2013)
- No antiemetic clinical effects demonstrated for SSRI's
Mechanisms of Actions of Enterra System:

1) Centrally acting anti-emetic-Thalamic and caudate lobe areas identified by PET Scan.
2) Increased vagal activity- associated increased fundic relaxation and food intake.
3) It does not change gastric emptying or electrical dysrhythmias
4) Abdominal pain is not a target
PAIN CONTROL IN GASTROPAREGESIS

- Recognition that abdominal pain can be present and is important symptom in GP patients
- Differential diagnosis for pain: Peptic ulcer disease, acute or chronic cholecystitis, gall bladder dyskinesia, IBS, SIBO, median arcuate ligament syndrome
- NSAID's, Tylenol, Tramadol preferred
- TCA, SSRI, SNRI (cymbalta), gabapentin, pregablin etc could be considered
- Avoid narcotics !!!!!!!
  - Role of narcotics-fentanyl patch, methadone
- Referral to pain management clinic
VR - VIRTUAL REALITY
The last 5 years- a new era in Gastroparesis - recognition of the role of the pylorus in pathophysiology - implications for diagnosis and therapy
Evolving pyloric based therapies for GP

Botox Injection into Pylorus for Gastroparesis

- LAPAROSCOPIC PYLOROPLASTY
  WITHOUT GES IMPROVED SYMPTOMS
  OF GASTROPARESIS

Heineke-Mikulicz Pyloroplasty

Fig. 4: Gastroparesic symptom scores before and 3 months after laparoscopic pyloroplasty.

J Gastrointestinal Surgery (2011) 15:1313-1319
THE BRAVE NEW WORLD FOR GASTROPARESIS- AN ENDOSCOPIC REVOLUTION

Key Remaining Question: Is GES Needed or will Pyloroplasty Alone suffice?

On going double-blind randomized trial of GES + Pyloroplasty at Texas Tech University HSC El Paso.
- The GES device is either “ON or “OFF” – symptoms and gastric emptying monitored for 3 months post-operatively
- Current status- 20 patients enrolled STAY TUNED FOR RESULTS OF THIS PIVOTAL STUDY
ROME III CRITERIA FOR ADULT CYCLIC VOMITING SYNDROME

- **Must include all of the following:**
  1. Stereotypical episodes of vomiting specifically regarding onset (acute) and duration (less than one week)
  2. Three or more discrete episodes in the prior year
  3. Absence of nausea and vomiting between episodes
  4. Severe abdominal pain initially in the epigastrium, radiating diffusely and beginning with the onset of nausea and vomiting

  
  
  * Supportive Criterion: History or family history of migraine headaches
# CANNABINOID HYPEREMESIS SYNDROME

<table>
<thead>
<tr>
<th>Definitions</th>
<th>History of long term cannabis use</th>
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<tr>
<td><strong>Major Features</strong></td>
<td>1. Cyclic episodes of nausea and vomiting and abdominal pain</td>
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<td>2. Reduction and/or resolution of symptoms after cannabis cessation</td>
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<td>3. Relief of symptoms with hot showers and baths</td>
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<td>4. Abdominal pain (epigastric or periumbilical)</td>
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<td></td>
<td>5. History of frequent—even daily use of marijuana</td>
</tr>
<tr>
<td><strong>Supportive Features</strong></td>
<td>1. Males dominate</td>
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<td></td>
<td>2. Patients usually less than 40 years of age</td>
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<td>3. Negative lab, radiology and EGD results</td>
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<td>4. Weight loss not a prominent feature</td>
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*McCallum et al, Pharmaceuticals 2012, 5, 719-726*
Long term outcome of adult CVS patients on TCA

41 patients (22 M) with mean age of 35 years (18 to 63) on tricyclic antidepressant (TCA) were able to be followed for 1 year and 23 were evaluated for 2 years.

The average dose range of TCA was 1-2 mg/kg QHS starting at 10-25 mg dose and increasing every 2-3 weeks as tolerated to achieve symptoms control to as high as 250 mg.

Additional supportive medications included: Lorazepam, Dicyclomine, anti-emetics, anti-migraine and PPI’s.

- Significantly reduces the frequency and duration of episodes, ED visits, and hospitalizations (P<0.05), and overall clinical well-being providing evidence that they are effective therapy for adult CVS.

THE “TEXTBOOK” PRESENTATION

• EFFORTLESS, FOUNTAIN-LIKE, AND REPETITIVE REGURGITATION OF GASTRIC CONTENTS WITHIN 5 TO 30 MINUTES OF INGESTION WITH EITHER RE-SWALLOWING OR SPITTING UP OF THE CONTENTS (NOT PROJECTILE)

• OCCURS FOR SOLIDS AND LIQUIDS

• THE REGURGITANT CONSISTS OF RECOGNIZABLE JUST INGESTED FOOD AND MAY HAVE A PLEASANT TASTE BUT ALSO ACCOMPANYING HEARTBURN

• OFTEN PRECEDED BY BELCHING OR BELCH SENSATION

• NAUSEA / WRETCHING DO NOT TYPICALLY PRECEDE THE REGURGITATION

• EPIGASTRIC PAIN-ABDOMINAL WALL PAIN (CARNETT SIGN) - IS PROMINENT

• “MEAL IN, MEAL OUT, DAY IN, DAY OUT” SETTING
PATHOPHYSIOLOGY

- Increased intra-abdominal pressure and LES relaxation
- Increased gastric sensitivity to balloon distention\(^1\)
- Adaptation of the belch reflex
- Self-induction of transient LES relaxations\(^2\)
- History of psychosocial issues – stress/depression
- History of a vomiting illness (conditioned vomiting)
- Essentially the stomach is “programmed”

\(^1\) Thumshirn, Camilleri et al Am J Physiol, 1998
\(^2\) Smout, Breumelhof, Am J Gastroenterol, 1990
**Figure 1:** Muscular mechanism of rumination by electromyography. Rumination (light blue arrow) occurs as a result of abdominal compression (orange arrow), coupled with chest expansion (green arrow). Electromyography showing increased intercostal activity and abdominal wall activation during rumination events (blue box).

**Figure 2:** Diaphragmatic breathing. (A) The patient slowly inhales through the nose while protruding the abdomen and keeping the chest stationary. (B) The patient slowly exhales via the mouth and allows the abdomen to retract. Emphasize on breathing out slowly and thoroughly (purse lips). This should be done prior, during, and after meals for 5-minute periods.
PHARMACOLOGICAL THERAPY

- PROTON PUMP INHIBITORS (BRIEFLY)
- TRICYCLICS – LOW DOSE – TO ADDRESS GASTRIC/FUNDIC SENSITIVITY, FULLNESS SENSATION AND PAINFUL ABDOMINAL MUSCLES FROM FREQUENTLY CONTRACTING
- TREAT EPIGASTRIC- ABDOMINAL WALL PAIN WITH LIDOCAINE PATCHES AND HOT PADS. (CARNETT TEST)
- ANTIEMETICS – AS BACK UP
- IDENTIFYING AND TREATING THE GASTROPARESIS GROUP
- GABBA RECEPTOR AGONIST – BACLOFEN
GASTROINTESTINAL MANIFESTATION OF HYPERMOBILITY SYNDROME BACKGROUND

- Generalized joint hypermobility (GJH) is common with ~ 10% of population
- More common in women
- Most people don’t develop any symptoms
- GJH can be identified in some well-defined inherited connective tissue disorders:
  - Ehlers-Danlos Syndrome
  - Benign joint hypermobility syndrome (BJHS)
  - Marfan syndrome
  - Osteogenesis imperfecta
UPPER GI SYMPTOMS IN HEDS

- Epigastric pain syndrome
- Postprandial distress syndrome
- Functional dyspepsia
- Functional vomiting
- Chronic idiopathic nausea
- Diffuse visceral hypersensitivity, affecting oral intake and nutritional status