Neutralizing the Acid: Treating Adult GERD/LPRD

SOHN Annual Congress 2012
Washington, DC
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Objectives
- Explain the incidence, pathophysiology, diagnosis, and treatment options for GERD/LPRD
- Discuss the pharmacological management – drugs, dosages, adverse reactions of GERD/LPRD medications
- Discuss the learning needs of the patients requiring treatment for GERD/LPRD
- Participate in an interactive discussion of GERD/LPRD treatment

Definition
- GERD – the retrograde flow of gastric contents into the esophagus causing troublesome symptoms and/or complications
- LPRD – the retrograde flow of gastric contents further into the upper aero-digestive tract causing symptoms and/or complications

Epidemiology
- Number 1 GI disorder
- Prevalence in Western countries approaching 20%
- From 1987-2007, prevalence increased by 4%/yr. in the Western world
- From 1992-2005, prevalence increased by 5% in North America
- Cost - $3355 per employee with 65% direct medical cost, Prescription cost 17%, indirect cost 19%
- No significant difference found in gender

Composed of hydrochloric acid, potassium chloride and sodium chloride
Produced by parietal cells in the fundic region
Unequal distribution of gastric acid after eating
Histamine released from ECL cells activates the H2 receptors which stimulate gastric acid secretion
H+/K+ ATPase proton pump is the transport protein responsible for regulating the release of hydrogen ions into the stomach
Neutralizing mechanisms occurring

Gastric Acid Production

Mucus production
Bicarbonate
Blood flow
Prostaglandins

Defensive mechanisms

Potential mechanisms of GERD/LPRD

History & Physical
Symptoms, frequency, occurrence after meal, bowel habits
BMI, hiatal hernia, abdominal girth
Examination
Laryngeal, Oropharyngeal appearance
Diagnostic tests
Laryngeal, Upper GI endoscopies, Multichannel intraluminal impedance pH monitoring, esophageal motility

Diagnosis
Signs & Symptoms - GERD
- Heartburn
- Regurgitation
- Dysphagia
- Odynophagia
- Increased salivation
- N&V, Abd. pain
- Chest Pain
- Bloating
- Sleep disturbance
- Gastric/Esophageal irritation or ulcers
- Esophageal strictures
- H-Pylori positive
- GastroEsophageal dysmobility findings
- Significant gastric findings

Signs & Symptoms - LPRD
- Chronic cough
- Hoarseness
- Asthma like symptoms
- Frequent throat clearing
- Feeling of throat clearing
- Post nasal drip
- Pain or sensation in throat
- Bad/bitter taste
- Red, irritated arytenoids
- Red, irritated larynx
- Small laryngeal ulcers
- Swelling of vocal folds
- Granulomas
- Possible significant laryngeal pathology
- Evidence of hiatal hernia

Treatment Options
- Lifestyle modifications
- Medications
- Surgical options

Lifestyle modifications
- Small frequent meals
- 2-3 hrs. before recumbent position
- Elevate HOB
- Avoid foods/drinks that trigger reflux
- Maintain healthy weight
- Avoid tight fitting clothes
- Avoid smoking
- Reduce stress
- Acupuncture

Medications
- Antacids
- H-2 Receptor Blockers
- Proton pump inhibitors
- Prokinetic agents
- Mucosal protective agents
- TLESR blockades

Surgical Options
- Nissen fundoplication
- Replacement sphincter valve – endoscopic
- Stretta procedure
- Linx procedure
**Medications**

**Antacids**
- NEUTRALIZES ACID and INHIBITS PEPSIN for Mild or Sporadic Symptoms
- Sodium Bicarbonate (Baking Soda, Alka-Seltzer)
- Calcium Carbonate (Rolaids, Tums)
- Magnesium Hydroxides (Milk of Magnesia)
- Aluminum Hydroxides (Alu-Cap, Amphojel)

**Antacid dosage**
- Available in suspensions or tablets
- Bypasses need to be systemically absorbed
- Quick action on an empty stomach, 1-3 hrs. if taken with food.
- Short duration, potency dependent on amt. of acid neutralization per dosage
- Frequent dosing
- 10% improvement in GERD symptoms

**Antacid Adverse Reactions**
- Dose related
- Sodium Bicarbonate – High sodium load, systemic alkalosis
- Calcium products – milk alkali syndrome (hypercalcemia, renal insufficiency, metabolic alkalosis)
- Magnesium products – diarrhea, hypermagnesemia with renal insufficiency
- Aluminum products – encephalopathy and osteomalacia in ESRD
- Drug interactions

<table>
<thead>
<tr>
<th>Constituent</th>
<th>Neutralizing Capacity</th>
<th>Salt formed in Stomach</th>
<th>Solubility of salt</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaHCO₃</td>
<td>High</td>
<td>NaCl</td>
<td>High</td>
<td>Systemic alkalosis, fluid retention</td>
</tr>
<tr>
<td>CaCO₃</td>
<td>Moderate</td>
<td>CaCl₂</td>
<td>Moderate</td>
<td>Hypercalcemia, nephrolithiasis, constipation</td>
</tr>
<tr>
<td>Al(OH)₃</td>
<td>High</td>
<td>AlCl₃</td>
<td>Low</td>
<td>Constipation, hypophosphatemia, drug absorption reduction, bone mineralization</td>
</tr>
<tr>
<td>Mg(OH)₂</td>
<td>High</td>
<td>MgCl₂</td>
<td>Low</td>
<td>Diarrhea, hypermagnesemia (in patients with renal insufficiency)</td>
</tr>
</tbody>
</table>
Alginate

- Algnate is an anionic polysaccharide
- Combined with bicarbonate
  - When contacted with gastric acid, it precipitates into a low density neutral gel.
  - The bicarbonate releases CO2 which is then trapped under the gel creating "raft"
  - If reflux occurs, the neutral raft protects esophagus

Histamine 2 Receptor Antagonist - H2RA

- Antagonist of histamine at the parietal cell H2 receptors
  - Cimetidine (Tagamet)
  - Ranitidine (Zantac)
  - Famotidine (Pepcid)
  - Nizatidine (Axid)

H2RAs

- Available over the counter or prescription
- Inverse agonists by decreasing functional activity of histamine
- Histamine normally adjusts the basal rate of acid release during nonfeeding times
- Absorbed in small intestine after oral administration
- Peak concentrations 1-3 hrs. not effected by food administration but can be by antacids
- Eliminated by renal mechanisms

H2RA dosing

- Once a day dosing at bedtime
- Effects on acid secretion decline with time
- Rebound acid secretion on drug cessation
- Better suited to symptom based on demand use but not effective in erosive esophagitis
- OTC dosing effective to reduce nocturnal acid for 12hr.
- Prophylactic use before meals

H2RA Adverse Reactions

- Cimetidine has particular issues with pharmacokinetics
- Reversible with drug discontinuation
- Gynecomastia & impotence
- Hematologic abnormalities
- CNS symptoms (esp. elders)
- Drug interactions - CYP inhibitor

Proton Pump Inhibitors - PPIs

- Most potent acid secretion inhibitor thru HK ATPase
  - Omeprazole (Prilosec)
  - Esomeprazole (Nexium)
  - Lansoprazole (Prevacid)
  - Pantoprazole (Protonix)
  - Rabeprazole (Aciphex)
  - Omeprazole IR (Zegerid)
  - Dexlansoprazole (Dexilant, Kapidex)
  - Tenatoprazole
**PPIs**

- Significantly more effective for healing and symptom relief (van Pinxteren, B & et al, 2006)
- Acid suppression overcome only by development of new proton pumps
- Do not have a rapid onset of action
- Plasma levels decrease 6-10 hrs. after ingestion
- Do not reduce the number of reflux episodes (Hemmink G & et al, 2008)

**PPI dosing**

- Formulations available as capsules, immediate release, delayed release, some formulations IV. OTC and prescription
- Takes 3 days to achieve maximum acid suppression
- Half life for early PPIs 1-2 hrs. with duration of action
- Longer elimination half life of newer PPIs could result in more activated PPI being present and available

**PPIs – Adverse Reactions**

- Headache
- Diarrhea
- Nausea/Vomiting
- Dizziness
- Pruritus/Rash
- Case reports of interstitial nephritis
- Hepatitis

**PPI Long Term Safety**

- Hip Fracture
  - Inhibit calcium absorption
  - Interfere with osteoclast function
  - Induce hypergastrinaemia resulting in reductions in bone mineral density related to hyper parathyroidism

**PPIs Long Term Safety-Hip Fractures**


- Regular use of PPIs was associated with increased risk of hip fracture among postmenopausal women, with the strongest risk observed in individuals with the longest duration of use or with a history of smoking
**PPIs Long Term Safety**
- Physiological hypergastrinemia does not cause gastric carcinoids or cancer
- The use of PPIs is associated with the development of fundic gland polyps
- Not associated with an increased risk of latent iron deficiency
- Short term use increases the risk of CAP but PPI use does not increase the risk of hospital acquired pneumonia

**PPI Long Term Safety**
- No convincingly proven data that PPIs increase the risk of Clostridium Difficile-associated pneumonia
- No proven adverse effect on the enteric microbiota, and if such an effect exists, no clinically important adverse effect.

**Prokinetics**
- **Metoclopramide (Reglan)**
  - Increase acetylcholine concentrations by antagonist of the M1 receptor and inhibiting acetylcholinesterase
  - Enhances GI motility by increasing small intestine contractions
  - Increases pressure on the LES

**Adverse Reactions**
- Restlessness, drowsiness, dizziness, fatigue, HA,
- Tardive dyskinesia

**Dosage**
- Short term use
- 4 times/day 30 min. before meals

**Mucosal Protective Agents**
- **Sulfuric Acid (Carnafate)**
  - Sulfated polysaccharide
  - Acid activated
  - Nonabsorbable medication which binds to the gastric mucosa and ulcerated tissue
  - Used in critically ill pts for prophylactic stress ulcer

**Adverse Reactions**
- Constipation, impairment of drugs
- Avoid in renal pts.

**Dosage**
- 1 hr. before meals and bedtime

**TLESR Blockades**
- GABA & GABAA receptor agonists
- Cholecystokinin A antagonists
- Morphine
- Glutamate antagonists
- Cannabinoids
- Metabotropic glutamate receptor agonists & antagonists
- Nitric oxide synthase inhibitors
Antisecretory drugs for the treatment of patients with esophageal GERD syndromes (healing esophagitis, symptomatic relief, and maintaining healing of esophagitis). In these uses, PPIs are more effective than H2RAs, which are more effective than placebo.

Long-term use of PPIs for the treatment of patients with esophagitis once they have proven clinically effective. Long-term therapy should be titrated down to the lowest effective dose based on symptom control.

Weight loss should be advised. Elevation of HOB should be advised, other lifestyle changes tailored to pt. conditions. Twice-daily PPI w/ esophageal syndrome unresponsive to once daily. Short course of PPIs for pts. with symptomatic esophageal syndrome w/o esophagitis. Acute or maintenance therapy with once or twice daily PPIs (or H2RAs) for pts. with suspected LPRD with esophageal syndrome.

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Grade A: Strongly Recommended Based on Good Evidence That It Improves Important Health Outcomes
- Antisecretory drugs for the treatment of patients with esophageal GERD syndromes (healing esophagitis, symptomatic relief, and maintaining healing of esophagitis). In these uses, PPIs are more effective than H2RAs, which are more effective than placebo.
- Long-term use of PPIs for the treatment of patients with esophagitis once they have proven clinically effective.
- Long-term therapy should be titrated down to the lowest effective dose based on symptom control.

Grade B: Recommended With Fair Evidence That It Improves Important Outcomes
- Weight loss should be advised
- Elevation of HOB should be advised, other lifestyle changes tailored to pt. conditions
- Twice-daily PPI w/ esophageal syndrome unresponsive to once daily
- Short course of PPIs for pts. with symptomatic esophageal syndrome w/o esophagitis
- Acute or maintenance therapy with once or twice daily PPIs (or H2RAs) for pts. with suspected LPRD with esophageal syndrome

Grade C: Balance of Benefits and Harms Is Too Close to Justify a General Recommendation
- Pts. with LPRD with persistant troublesome symptoms despite PPI therapy should be considered for antireflux surgery. Potential benefits outweigh effects from surgery

Grade D: Recommend Against, Fair Evidence That It Is Ineffective or Harms Outweigh Benefits
- Metoclopramide as therapy for GERD/LPRD
- Once or twice daily PPIs (or H2RAs) for acute treatment of pts. with LPRD & no GERD symptoms

Grade Insuff: No Recommendation, Insufficient Evidence to Recommend for or Against
- Broadly advocating lifestyle modifications for all GERD/LPRD pts.
- Adding H2RAs as nocturnal dose for pts. with inadequacy control of symptoms to twice daily PPIs
- Maintenance therapy with PPIs (or H2RAs) for LPRD w/o GERD symptoms
- Once or twice daily PPIs for pts. with suspected reflux cough syndrome
- Advocating bone density, calcium supplements, H pylori screening or other precaution because of PPI use

Summary
- PPIs are best choice
- Some Lifestyle modifications may be advocated
- Guidelines are available
- More research is needed
Questions/Discussion

Thank You