Gastroesophageal Reflux Disease (GERD)
TH 5001 Therapeutics III
Fall 2003
Kristi L. Theobald, Pharm.D., BCPS
ktheobald@stlcop.edu
314-407-7204 (pager)
314-446-8537 (office phone)

Required Reading:

Supplemental Reading:

Ability Outcomes:
Assess a patient with GERD.
Evaluate drug therapy in a patient with GERD.
Select/Recommend drug therapy for a patient with GERD.
Monitor for expected therapeutic outcomes and potential adverse effects associated with drug therapy for GERD.
Educate patients, care givers and health care professionals regarding drug therapy used in the management of GERD.
Collaborate with peers to devise a patient-specific therapeutic plan for the management of GERD.
Communicate the information pertinent to the management of GERD in a clear, concise and organized manner.

Content Questions:
1. Define GERD and gastroesophageal reflux.
2. Explain the role of the lower esophageal sphincter (LES) in GERD.
3. List foods and medications that affect LES pressure.
4. Identify direct irritants to the esophageal mucosa.
5. Describe typical and atypical clinical manifestations of GERD.
6. Explain how GERD is diagnosed.
7. Discuss the nonpharmacologic treatment options for GERD.
8. Discuss the pharmacologic treatment options for phase I, II and III of GERD.
9. Understand the advantages and disadvantages for each of the medications used in the treatment of GERD.
10. Discuss the mechanisms of action, dosing, adverse effects and drug interactions for each of the medications used in the treatment of GERD.
11. Understand the role of combination therapy in the management of GERD.
12. Discuss treatment options for maintenance therapy in GERD.
Gastroesophageal Reflux Disease (GERD)

Introduction/Epidemiology
- Approximately 10% of Americans suffer from heartburn on a daily basis and more than 1/3 have intermittent symptoms.
- Up to 46% of patients heal spontaneously with self-medication and another 31% show significant improvement.
- Mortality is low (1 death per 100,000 patients); however, quality of life is impacted significantly.

Definitions
- GERD
  - Any symptomatic clinical condition or histologic alteration that results from episodes of gastroesophageal reflux.
- Gastroesophageal reflux
  - The retrograde movement of gastric contents from the stomach into the esophagus.

Pathophysiology
- Defective lower esophageal sphincter (LES) pressure
  - Spontaneous transient LES relaxations
  - Transient increases in intra-abdominal pressure
  - Atonic LES
- Impaired mucosal defense mechanisms
  - Anatomic factors
  - Prolonged esophageal clearance
  - Decreased mucosal resistance
  - Delayed gastric emptying
- Aggressive factors
  - Gastric acid, pepsin, bile acids and pancreatic enzymes

| FOODS AND MEDICATIONS THAT MAY WORSEN GERD SYMPTOMS |
|---------------------------------|---------------------------------|---------------------------------|
| **Decrease LES pressure**       | **Foods**                       | **Medications**                 |
|                                 | Peppermint, spearmint           | Anticholinergics                |
|                                 | Chocolate                       | Barbiturates                    |
|                                 | Coffee, tea, cola               | Benzodiazepines                 |
|                                 | Fatty meal                      | Caffeine                        |
|                                 | Garlic                          | Dihydropyridine CCBs            |
|                                 | Onions                          | Dopamine                        |
|                                 |                                 | Estrogen                        |
|                                 |                                 | Ethanol                         |
|                                 |                                 | Isoproterenol                   |
|                                 |                                 | Narcotics                       |
|                                 |                                 | Nicotine (smoking)              |
|                                 |                                 | Nitrates                        |
|                                 |                                 | Phentolamine                    |
|                                 |                                 | Progesterone                    |
|                                 |                                 | Theophylline                    |

**Direct irritant to the esophageal mucosa**
- Spicy foods
- Orange juice
- Tomato juice
- Coffee
- Alendronate
- Aspirin
- Iron
- NSAIDs
- Quinidine
- Potassium chloride
Clinical Manifestations

- “Heartburn”
  - Uncomfortable, hot or burning sensation located beneath the sternum
  - Waxing and waning in character
  - Often radiates up the chest, sometimes into the throat or back
  - Worsened by the supine position, bending over or eating a high-fat meal
  - Most commonly reported when gastric pH < 4

- Water brash
- Belching, regurgitation
- Symptoms generally improve with use of antacids
- Atypical symptoms
  - Nonallergic asthma
  - Chronic cough
  - Hoarseness
  - Pharyngitis
  - Chest pain that mimics angina

- Symptoms indicative of complicated disease

- Severity of symptoms usually does not correlate with the degree of esophagitis but it does correlate with the duration of reflux

Diagnosis

- CLINICAL HISTORY
  - Extensive diagnostic work-up usually is not required. If the patient's history is typical for uncomplicated GERD, empiric treatment is appropriate.
  - Further diagnostic testing should be performed in the following patients:

- Endoscopy is the primary technique used to confirm a diagnosis of GERD

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>Normal esophageal mucosa</td>
</tr>
<tr>
<td>Grade 1</td>
<td>Erythema or diffusely red mucosa, edema, causing accentuated folds</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Isolated round or linear erosions extending from the gastroesophageal junction upward and not involving entire circumference</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Confluent erosions extending around entire circumference or superficial ulceration without stenosis</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Complicated cases; erosions as above plus deep ulcerations, strictures or columnar epithelium-lined esophagus</td>
</tr>
</tbody>
</table>

- Ambulatory pH testing
  - Indicated in the following patients:
    - Continuous symptoms without evidence of esophageal damage
    - Refractory to standard drug therapy
    - Atypical symptoms
  - Documents the pattern, frequency and duration of acid reflux
  - Seeks to correlate a patient’s symptoms with either normal or abnormal esophageal acid exposure
  - Most clinically applicable variable is the total percentage of the monitoring period that esophageal pH is below 4
Treatment

- Goals of therapy
  - Alleviate or eliminate the patient’s symptoms
  - Decrease the frequency or recurrence and duration of gastroesophageal reflux
  - Promote healing of the injured mucosa
  - Prevent the development of complications

- Non-pharmacologic therapy/lifestyle modifications
  - Elevate the head of the bed 6 to 10 inches
    - Blocks under the head of the bed
    - Under mattress foam wedge
  - Dietary changes
    - Avoid foods that may decrease LES pressure (see table)
    - Avoid foods that have a direct irritant effect on the esophageal mucosa (see table)
    - Include protein-rich meals in diet
    - Eat small meals and avoid eating within 3 hours of sleeping
    - Weight loss
  - Smoking cessation
  - Avoid alcohol
  - Avoid tight-fitting clothes
  - Discontinue drugs that may decrease LES pressure
  - Take drugs that have a direct irritant effect on the esophageal mucosa with plenty of liquid if they cannot be avoided

- Pharmacologic therapy

<table>
<thead>
<tr>
<th>Patient Presentation</th>
<th>Treatment Regimen</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>Lifestyle modifications PLUS Antacids ± alginic acid AND/OR Low dose OTC H2-blocker (up to BID)</td>
<td>- Lifestyle changes should be started initially and continued throughout the course of treatment. - If symptoms are unrelieved with lifestyle modifications and OTC medications after 2 weeks, begin pharmacologic therapy (phase II).</td>
</tr>
<tr>
<td>Intermittent, mild heartburn</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase II</td>
<td>Lifestyle modifications PLUS Standard dose H2-blockers for 6-12 weeks OR Proton pump inhibitors for 4-8 weeks</td>
<td>- For typical symptoms, treat empirically with phase II therapy. - Mild GERD can usually be treated effectively with H2-blockers. - Patients with moderate to severe symptoms should receive a proton pump inhibitor as initial therapy. - If symptoms are relieved, treat recurrences on an as-needed basis. If symptoms recur frequently, consider maintenance therapy with the lowest effective dose (generally standard doses).</td>
</tr>
<tr>
<td>Symptomatic relief of GERD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase II</td>
<td>Lifestyle modifications PLUS Proton pump inhibitors for 8-16 weeks (up to BID) OR High dose H2-blockers for 8-12 weeks</td>
<td>- Patients not responding to phase II therapy, including those with persistent atypical symptoms should be evaluated via 24-hour pH monitoring to confirm diagnosis of GERD. If present, consider phase III therapy. - Proton pump inhibitors are the most effective maintenance therapy in patients with atypical symptoms, complicated symptoms and erosive disease.</td>
</tr>
<tr>
<td>Healing of erosive esophagitis or treatment of patients with moderate to severe symptoms or complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase III</td>
<td>Antireflux surgery</td>
<td>- Goal is to reestablish the antireflux barrier, to position the LES within the abdomen where it is under positive pressure and to reduce the hiatal hernia.</td>
</tr>
</tbody>
</table>

Therapeutic Approach to GERD
Specific Agents

- **Antacids**
  - **Mechanism of action**
    - Neutralizes the gastric pH decreasing the activation of pepsin from pepsinogen
    - Neutralization of gastric fluid also leads to an increased LES
  - **Dosing**
    - Variable, usually 2 tablets or 1 tablespoonful QID
  - **Adverse effects**
    - 
  - **Drug Interactions**
    - Numerous including fluoroquinolones, tetracyclines, oral iron preparations, digoxin, isoniazid, ketoconazole, itraconazole, etc.

- **Alginic acid**
  - **Mechanism of action**
    - Forms a highly viscous solution that floats on the surface of the gastric contents
    - Acts as a protective barrier for the esophagus
    - Reduces the frequency of reflux episodes
  - **Dosing**
    - Usually 2 tablets QID
  - **Adverse effects/drug interactions (similar to antacids)**

- **Sucralfate**
  - **Mechanism of action**
    - Undergoes extensive cross-linking and polymerization in the presence of acid to produce a viscous, sticky gel that adheres strongly to epithelial cells and even more strongly to ulcer craters
    - Inhibits pepsin activity
    - Aluminum moiety stimulates endogenous prostaglandins and binds bile salts and phosphate in the GI tract
  - **Dosing**
    - 1 gram QID (on an empty stomach)
  - **Adverse effects**
    - 
  - **Drug interactions**
    - Numerous including digoxin, ketoconazole, levothyroxine, phenytoin, fluoroquinolones, tetracyclines, theophylline, warfarin, etc.

- **H₂-blockers**
  - **Mechanism of action**
    - Competitively inhibit the actions of histamine at the H₂-receptors of the parietal cell; the most prominent effects of H₂-blockers are on basal acid secretion
  - **Dosing (OTC)**
    - Cimetidine 200mg po (up to BID)
    - Famotidine 10mg po (up to BID)
    - Nizatidine 75mg po (up to BID)
    - Ranitidine 75mg po (up to BID)
  - **Dosing (prescription, standard)**
    - Cimetidine 400mg BID
    - Famotidine 20mg BID
    - Nizatidine 150mg BID
    - Ranitidine 150mg BID
Dosing (prescription, high)
- Cimetidine 400mg QID or 800mg BID
- Famotidine 40mg BID
- Nizatidine 150mg QID or 300mg BID
- Ranitidine 150mg QID or 300mg BID

Adverse effects

Drug interactions
- All H₂-blockers decrease the absorption of ketoconazole and itraconazole
- Cimetidine may inhibit the metabolism of theophylline, warfarin, carbamazepine, phenytoin, nifedipine, propranolol, tricyclic antidepressants, etc.

Proton pump inhibitors (PPIs)
- Mechanism of action
  - "Prodrugs" that require activation in an acidic environment
  - Covalently bind to H⁺/K⁺-ATPase (proton pump), the final pathway for acid secretion, resulting in a profound and prolonged suppression of gastric acid secretion
- Dosing
  - Esomeprazole 20-40mg QD
  - Lansoprazole 15-30mg QD (enteric-coated granules)
  - Omeprazole 20mg QD (enteric-coated granules)
  - Pantoprazole 40mg QD
  - Rabeprazole 20mg QD
  - Up to BID in resistant cases
  - Take 15-30 minutes before breakfast to maximize efficacy
  - In patients unable to swallow, the contents of the lansoprazole or omeprazole capsule can be mixed in applesauce or placed in orange juice OR a suspension can be prepared for nasogastric/nasoduodenal use by dissolving the granules in an 8.4% solution of sodium bicarbonate
- Adverse effects
  - Somnolence, nervousness, fatigue, dizziness, weakness, depression, diarrhea and rash
  - Parkinsonian symptoms, tardive dyskinesia and akathisia
- Drug interactions
  - All PPIs decrease the absorption of ketoconazole and itraconazole
  - Omeprazole has the potential to inhibit the metabolism of warfarin, diazepam and phenytoin (CYP2C19)

Metoclopramide
- Mechanism of action
  - Increases LES pressure and accelerates gastric emptying
- Dosing
  - 10mg QID
- Adverse effects
  - Somnolence, nervousness, fatigue, dizziness, weakness, depression, diarrhea and rash
  - Parkinsonian symptoms, tardive dyskinesia and akathisia
- Drug interactions
  - Anticholinergics and narcotics may antagonize GI effects
Bethanechol
- **Mechanism of action**
  - Stimulates cholinergic receptors that increase LES tone, esophageal clearance and peristalsis
- **Dosing**
  - 10-50mg TID-QID
- **Adverse effects**
  - Abdominal cramps, diarrhea, blurred vision, flushing, diaphoresis, salivation, nausea and vomiting, urinary frequency, shortness of breath, hypotension

Cisapride
- No longer available for routine use because of life-threatening arrhythmias when combined with certain medications and other disease states

**Combination Therapy**
- Acid-suppressing agent (H₂-blocker or PPI) *plus* metoclopramide
  - Only indicated in a patient with GERD who has a known or suspected motility disorder or in a patient who has failed high-dose PPI
- PPI *plus* H₂-blocker
  - In patients experiencing nocturnal acid reflux on twice daily PPI, addition of an H₂-blocker at bedtime can abolish this breakthrough period
    - No clear clinical benefit demonstrated yet

**Maintenance Therapy**
- Approximately 70-90% of patients will relapse within 1 year of discontinuation of therapy regardless of what therapeutic regimen is used
- H₂-blockers may be effective maintenance therapy for patients with *mild* disease
  - Only FDA-approved maintenance regimen is ranitidine 150mg BID
- PPIs are the drugs of choice for maintenance treatment of moderate to severe esophagitis
  - For most patients, the dose of PPI necessary to maintain remission is at least the dose required to heal the acute esophagitis

**Special Populations**
- Atypical symptoms
  - Endoscopy
  - Empiric PPI
  - Ambulatory pH testing (if no response to phase II therapy)
- Endoscopy-negative reflux disease
  - Ambulatory pH testing
  - “Therapeutic trial” with a PPI

**Complications**
- Esophageal strictures
  - Form when reflux-induced ulceration stimulates fibrous tissue production and collagen deposition in the esophagus
  - Typically cause slowly progressive dysphagia for solid foods, such as meats and breads
- Barrett's esophagus
  - Condition in which a metaplastic columnar epithelium replaces squamous epithelium in the distal esophagus
  - Sequela of reflux esophagitis in most cases and a strong risk factor for adenocarcinoma of the esophagus and gastroesophageal junction
- Hemorrhage