1. GI Pharmacology - Acid Suppression: Antacids, Acid Suppressa...

GI Pharmacology
Acid Suppression: Antacids, Acid Suppressants, and Prokinetics

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2007

2. Objectives

Objectives

- Illustrate drug mechanisms of action
- Identify most common drug side effects
- Describe goals of therapy
3. Physiology of Gastric Acid Secretion

Physiology of Gastric Acid Secretion

- Parietal cell
  - Primary acid producing cell
    - Located in body & fundus of stomach
  - H⁺/K⁺ ATPase pump
    - Generates largest ion gradient known in vertebrates
  - Influenced by:
    - Acetylcholine, Histamine, Gastrin, Prostaglandins

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4. Physiology of Gastric Acid Secretion


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5. Physiology of Gastric Acid Secretion

Physiology of Gastric Acid Secretion

- Normal stomach pH:
  - Basal acid: approximately 1-2
  - Post prandial: 4-5 (x 1 hour)
    - Which in turn stimulates greater acid production

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6. Gastric Defense

Gastric Defense

- Tight junctions
  - Between gastric epithelial cells
- Mucin layer
  - Overlying cells
- Bicarbonate ion
  - Secreted into mucin layer
- Prostaglandins
  - Stimulate mucus production, bicarb, mucosal blood flow

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7. Drugs For Control of Gastric Acidity

Drugs For Control of Gastric Acidity

- Antacids
- Cytoprotectants
- H-2 receptor antagonists
- Proton pump inhibitors

8. Antacids

Antacids

- Mechanism:
  - Local neutralization of acid

- Components:
  - Aluminum hydroxides; Al(OH)₃
  - Magnesium hydroxides; Mg(OH)₂
  - Calcium carbonate; CaCO₃
  - Sodium bicarbonate; NaHCO₃
9. Antacids

Antacids

• Adverse effects:
  – Diarrhea - Mg$^{2+}$
  – Constipation - Al$^{3+}$
  – Abdominal distension, reflux - CaCO$_3$

• Cautions:
  – Renal insufficiency
  – Drug interactions

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10. Antacids

Antacids

• Milk-alkali syndrome
  – NaHCO$_3$ and/or CaCO$_3$ + dairy products
  – Excess Ca$^{2+}$ & absorbable alkali
    • Hypercalcemia
    • Reduced PTH
    • Phosphate retention
    • Calcium precipitates in kidney

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11. Antacid Examples

Antacid Examples
(mg per tablet or 5 mL)

<table>
<thead>
<tr>
<th>Product</th>
<th>Al(OH)₃</th>
<th>Mg(OH)₂</th>
<th>CaCO₃</th>
<th>Simethicone</th>
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</thead>
<tbody>
<tr>
<td>Mylanta</td>
<td>0</td>
<td>150</td>
<td>350</td>
<td>0</td>
</tr>
<tr>
<td>Mylanta ES</td>
<td>400</td>
<td>400</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>Maalox Max Str</td>
<td>400</td>
<td>400</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>MOM</td>
<td>0</td>
<td>400</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tums</td>
<td>0</td>
<td>0</td>
<td>750</td>
<td>0</td>
</tr>
</tbody>
</table>

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12. Cytoprotectants

Cytoprotectants

- Sucralfate
- Misoprostol
- Bismuth compounds

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13. Physiology of Gastric Acid Secretion

![Diagram of Physiology of Gastric Acid Secretion](image)

14. Cytoprotectants

**Cytoprotectants**

- **Sucralfate**
  - Sulfated polysaccharide
    - Also contains Al(OH)$_3$
  - Adheres to epithelial cells and ulcer craters
    - Activated by acidic environment
    - Lasts up to 6 hours
15. Sucralfate

Sucralfate

- Typical dose:
  - 1g by mouth 2-4 x/day
    - 30 min prior to eating

- Uses:
  - Acid-peptic disease
    - Role diminished in recent years
  - Stress ulcer prophylaxis

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16. Sucralfate

Sucralfate

- Adverse effects:
  - Constipation - most common (2%)
  - Accumulation of Al\(^{3+}\)
    - Caution if renal insufficiency
  - Drug interactions
    - Separate:
      - Usually 2 hours after other drugs

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17. Cytoprotectants

Cytoprotectants

• Misoprostol
  – Prostaglandin E1 analog
    • Stimulates secretion of mucin & bicarb
    • Increases mucosal blood flow
    • Suppresses acid production in parietal cell by binding to EP3 receptor

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18. Misoprostol

Misoprostol

• Typical dose:
  – 100 - 200 mcg by mouth 2-4 x/day
    • With food

• Uses:
  – Prevent NSAID-related mucosal damage

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19. Misoprostol

Misoprostol

- Adverse effects:
  - Diarrhea - up to 30%
    - With or without abdominal pain/cramps
  - Increased uterine contractility
    - Contraindicated in pregnancy
    - Used in combination with mifepristone or methotrexate for medical termination of pregnancy

20. Cytoprotectants

Cytoprotectants

- Bismuth compounds
  - Bind to base of ulcers
    - Also promote mucin & bicarb production
    - Have antibacterial effects
  - Example:
    - Bismuth subsalicylate
21. Bismuth subsalicylate

Bismuth subsalicylate

- Typical dose:
  - 2 tablespoonfuls or 2 tablets
    - Every 1/2-1 hour as needed
    - Max 4-8 doses/24 hours (reg vs max str)

- Adverse effects:
  - Darkening of tongue and/or stool
  - Constipation
  - Avoid if aspirin allergy

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22. H2-Receptor Antagonists

H2-Receptor Antagonists

- Cimetidine
- Ranitidine
- Famotidine
- Nizatidine

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23. Physiology of Gastric Acid Secretion

![Diagram of Physiology of Gastric Acid Secretion]


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24. H2-Receptor Antagonists

**H2-Receptor Antagonists**

- **Mechanism:**
  - Compete with histamine for binding to H2 receptors on parietal cells
  
  *More potent, longer-lasting effects than traditional antacids*

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25. H2-Receptor Antagonists

**H2-Receptor Antagonists**

- **Uses:**
  - Gastric & duodenal ulcers
  - Uncomplicated GERD
  - Stress ulcer prophylaxis

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26. H2-Receptor Antagonists

**H2-Receptor Antagonists**

- **Typical doses:**
  - Cimetidine
    - 200 - 400 mg 2-4 x/day
  - Ranitidine
    - 150 mg 1-2 x/day
  - Famotidine
    - 20 mg 1-2 x/day
  - Nizatidine
    - 150 mg 1-2 x/day

H2As should be dose adjusted for renal insufficiency

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27. **H2-Receptor Antagonists**

**H2-Receptor Antagonists**

- **Drug interactions:**
  - **Absorption:**
    - Drugs requiring acidic environment
      - Ketoconazole, Itraconazole, Didanosine
  - **Hepatic - Cimetidine**
    - Inhibitor of CYP-450:
      - Phenytoin, Theophylline, Warfarin

28. **H2-Receptor Antagonists**

**H2-Receptor Antagonists**

- **Adverse effects:**
  - **General:** Diarrhea, headache, drowsiness, fatigue, constipation
  - **Bone marrow suppression**
  - **CNS - seen more w/IV use**
    - Confusion, delirium, hallucinations, slurred speech
  - **Cimetidine**
    - Gynecomastia in men, galactorrhea in women
29. Proton Pump Inhibitors

Proton Pump Inhibitors

- Omeprazole
- Lansoprazole
- Rabeprazole
- Pantoprazole
- Esomeprazole

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30. Physiology of Gastric Acid Secretion

Physiology of Gastric Acid Secretion

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31. Proton Pump Inhibitors

Proton Pump Inhibitors

- **Mechanism:**
  - Prodrugs that require activation (protonation) in acidic environment
    - But parent compound unstable in acid
    - Enteric coated formulations usually required
  - Irreversibly bind to & inactivate $\text{H}^+\text{K}^+\text{ATPase}$

32. Proton Pump Inhibitors

Proton Pump Inhibitors

- **Pharmacokinetics**
  - Plasma half-life:
    - About 1-2 hours
  - Onset:
    - Full effects may take up to 2-5 days
  - Duration of effect:
    - Lasts 24-48 hours
33. Proton Pump Inhibitors

Proton Pump Inhibitors

• Uses:
  – Gastric & duodenal ulcers
  – GERD
  – Zollinger-Ellison syndrome

34. Proton Pump Inhibitors

Proton Pump Inhibitors

• Typical doses
  – Omeprazole or Esomeprazole
    • 20 - 40 mg/day
  – Lansoprazole
    • 15 - 30 mg/day
  – Rabeprazole
    • 20 mg/day
  – Pantoprazole
    • 20 - 40 mg/day
35. Proton Pump Inhibitors

Proton Pump Inhibitors

- Adverse effects:
  - Nausea, diarrhea, abdominal pain, constipation
  - Myopathy, arthralgia, headache
  - Skin rashes
  - Reduced vit B12 absorption
  - ECL cell hyperplasia (& gastric tumors?)
    - Hypergastrinemic state

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36. Sites of Drug Action

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37. Prokinetic Agents

Prokinetic Agents

- Cholinergic agents
  - Bethanechol
- Serotonin receptor modulators
  - Metoclopramide
  - Cisapride
  - Tegaserod
- Dopamine receptor blockers
  - Domperidone
  - Metoclopramide
- Motilin-like agents

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38. Physiology of Gastric Motility

Physiology of Gastric Motility


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39. Therapeutic Application

Therapeutic Application

- Ulcers due to *Helicobacter pylori*
  - Gram negative rod
  - Associated with gastritis
    - And subsequent gastric & duodenal ulcers
  - Maybe also some association with:
    - Gastric adenocarcinomas
    - Gastric B-cell lymphoma
    - Controversial

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40. Urease Breath Test for H. pylori

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Helicobacter pylori

**Helicobacter pylori**

- Treatment: Eradication
  - Multiple antimicrobials
  - Plus acid suppressive therapy

  - If nonulcer dyspepsia:
    - Eradication typically does not improve symptoms

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Helicobacter pylori

**Helicobacter pylori**

- Potential regimens:
  - 2 to 3 of the following:
    - Amoxicillin 1000 mg (2x/day)
    - Clarithromycin 500 mg (2x/day)
    - Metronidazole 500 mg (2-3x/day)
    - Tetracycline 500 mg (4x/day)
    - Bismuth subsalicylate (4x/day)

  - Plus high dose acid suppressive therapy

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43. Helicobacter pylori

**Helicobacter pylori**

- **Treatment duration:**
  - Typically 10-14 days for antibiotics
  - Acid suppressive therapy continued x 1 month with dose reduction

- **Adverse effects:**
  - Nausea, diarrhea, taste disturbances, allergic reactions

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