Treatment of Peptic Ulcer

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What is Peptic Ulcer?

- A peptic ulcer disease or PUD is an ulcer (defined as mucosal erosions equal to or greater than 0.5 cm) of an area of the gastrointestinal tract exposed to the acid and pepsin secretion.

- Gastritis is the precursor to PUD and it is clinically difficult to differentiate the two.
  - Stomach (called gastric ulcer)
  - Duodenum (called duodenal ulcer)
  - Esophagus (called Esophageal ulcer)
  - Meckel's Diverticulum (called Meckel's Diverticulum ulcer)
Damaged Mucosal Tissue in Peptic Ulcer Disease
Peptic Ulcer Disease

- Factors Increasing
  - *H. pylori*
  - NSAIDs
  - Acidic agents
  - Pepsin
  - Smoking

- Factors Decreasing
  - Mucus production
  - Buffers
  - Blood flow
  - Prostaglandins
Because of Imbalance

- Imbalance primarily between Aggressive factors and Defensive factors:

- Aggressive factors, e.g., acid, pepsin, bile etc.

- Defensive factors, e.g., mucus, HCO3, PG
Therapy is directed at enhancing host defense or eliminating aggressive factors; i.e., H. pylori
# Phases of gastric secretion

<table>
<thead>
<tr>
<th>Phase</th>
<th>Stimuli</th>
<th>Pathway</th>
</tr>
</thead>
</table>
| Cephalic (stimulate)   | Sight, smell, taste or thought of food       | 1) Vagus (M3 receptors)  
2) Histamine (H2 receptor)  
3) Gastrin |
| Gastric (stimulate)    | Food in the stomach                          | 1) Stretch: local reflex (M3 receptors)  
2) Chemical substances in food (gastrin)  
3) Increase pH: Inhibition of somatostatin (GHIH) release |
| Intestinal (inhibit)   | Chyme in the duodenum                        |                                                                         |
Proglumide

ACh

PGE$_2$

Histamine

Gastrin

Adenyl cyclase

ATP

cAMP

Protein Kinase
(Activated)

Ca$^{++}$

PGE receptor

M$_3$

Proton pump

K$^+$

H$^+$

Gastric acid

Parietal cell

Lumen of stomach

Antacid

Omeprazole

Misoprostol

Ranitidine

Proglumide

Gastrin receptor

Gastrin receptor

Gastrin

Antacid

Omeprazole

Misoprostol

Ranitidine

Proglumide
Antacids

Capsules & Tablets:
- Powders
- Chewable tablets
- Suspensions
- Effervescent granules and tablets
Antacids

- Weak bases that neutralize acid
- Also inhibit formation of pepsin
  (As pepsinogen converted to pepsin at acidic pH)
- Present day antacids:
  Aluminium Hydroxide
  Magnesium Hydroxide
- Not part of Physician prescribed regimen
- OTC drug for symptomatic relief of dyspepsia
Duration of action:
- 30 min when taken in empty stomach
- 2 hrs when taken after a meal

Side effects:
- $\text{Al}^{3+}$ antacids – constipation (As they relax gastric smooth muscle & delay gastric emptying)
- $\text{Mg}^{2+}$ antacids – Osmotic diarrhea.
- In renal failure $\text{Al}^{3+}$ antacid – Aluminium toxicity & Encephalopathy
Antacids – Common additives

- Simethicone – Decrease surface tension, thereby reduce bubble formation. Added to prevent reflux.
- Alginates – Form a layer of foam on top of gastric contents & reduce reflux.

**Oxethazaine:** Surface anaesthetic

Other types of antacids?
Antacids

- Aluminum salts
- Magnesium salts
- Calcium salts
- Sodium bicarbonate

Used alone or in combination
Antacid - Interactions

- Adsorb drugs and form insoluble complexes that are not absorbed.

Clinical importance:

Interactions can be avoided by taking antacids 2 hrs before or after ingestion of other drugs.
Now answer this question

- Is it rational to combine aluminium hydroxide and magnesium hydroxide in antacid preparations?
Combination provides a relatively fast and sustained neutralizing capacity.

(Magnesium Hydroxide – Rapidly acting
Aluminium Hydroxide – Slowly acting)

Combination preserves normal bowel function.

(Aluminium Hydroxide – constipation
Magnesium hydroxide – diarrhea)
Histamine H₂ Receptor Antagonist

- Reversible competitive inhibitors of H₂ receptor
- Highly selective, No action on H₁ or H₃ receptors
- Very effective in inhibiting nocturnal acid secretion (as it depends largely on Histamine)
- Modest impact on meal stimulated acid secretion (As it depends on gastrin, acetyl choline and histamine)
H₂ antagonists

- **Kinetics:**
  - All drugs are absorbed orally adequately
  - Bioavailability up to 80%
  - Absorption is not interfered by presence of food
  - Can cross placental barrier and reaches milk
  - Poor CNS penetration
  - 2/3rd of the drugs are excreted unchanged in bile and urine

- **Preparations:** available as tablets, injections
<table>
<thead>
<tr>
<th></th>
<th>Cimetidine</th>
<th>Ranitidine</th>
<th>Famotidine</th>
<th>Nizatidine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>80</td>
<td>50</td>
<td>40</td>
<td>&gt;90</td>
</tr>
<tr>
<td>Relative Potency</td>
<td>1</td>
<td>5 -10</td>
<td>32</td>
<td>5 -10</td>
</tr>
<tr>
<td>Half life (hrs)</td>
<td>1.5 - 2.3</td>
<td>1.6 - 2.4</td>
<td>2.5 - 4</td>
<td>1.1 - 1.6</td>
</tr>
<tr>
<td>Duration of action (hrs)</td>
<td>6</td>
<td>8</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Inhibition of CYP 450</td>
<td>1</td>
<td>0.1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dose mg(bd)</td>
<td>400</td>
<td>150</td>
<td>20</td>
<td>150</td>
</tr>
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</table>
• SMOKING has been shown to decrease the effectiveness of H₂ blockers
H₂ Blockers–Side effects & Interactions

- Extremely safe drugs

- Cimetidine causes gynecomastia, galactorrhea
  
  (as it is antiandrogenic (inhibit binding of dihydrotestosterone to androgenic receptor and inhibit meta of estradiol) & increases prolactin level)

- Cimetidine inhibits CYP450 & increases conc. of Warfarin, Theophylline, Phenytoin, Ethanol. Also causes confusion & headache in elderly patients.
Now answer this question

- What are the differences between cimetidine & famotidine
Proton Pump Inhibitors

- Most effective drugs in antiulcer therapy
- Irreversible inhibitor of $\text{H}^+ \text{K}^+\text{ATPase}$
- Prodrugs requiring activation in acid environment
- Acid secretion resumes only after synthesis of new molecules
<table>
<thead>
<tr>
<th>Proton Pump Inhibitors</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>20 mg o.d.</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>20 - 40 mg o.d.</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>30 mg o.d.</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>40 mg o.d.</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>20 mg o.d.</td>
</tr>
</tbody>
</table>
Poton Pump Inhibitors – Kinetics

- Given as enteric coated granules in capsule or enteric coated tablets
- Pantoprazole also given intravenously
- Half life – 1.5 hrs
- Since it requires acid for activation - given 1 hr before meals

Other acid suppressing agents not coadministered
Now answer this question

- It is given in the previous slides that the half life of proton pump inhibitors is 1.5 hours only and these drugs are generally given once daily. How this can be justified?
P.P.I. – Side effects & Interactions

- Extremely safe drugs
- Causes hypergastrinemia which leads to carcinoid tumor in rats?
- But no evidence of such tumors in man
- Inhibit CYP 450 & hence the metabolism of warfarin, phenytoin, etc
- Pantoprazole & Rabeprazole have no significant interactions
Note: long-term use may increase the risk of gastric neoplasia

a. When acid secretion is reduced gastrin is released as a normal homeostatic response, this stimulates the growth of the gastric epithelium including enterochromaffin cells which transform into carcinoid tumor.

b. Prolonged hypochlorhydria favours the colonization of the stomach by bacteria which have potential to convert ingested nitrates into carcinogenic nitrosamines.
Mucosal Protective Agents
Mucosal Protective Agents

- Sucralfate
- Misoprostol
Sucralfate

- Salt of sucrose complexed to sulfated aluminium hydroxide
- In acidic pH polymerises to viscous gel (as a paste) that adheres to ulcer base
- Taken on empty stomach 1 hr. before meals
- Concurrent antacids, H$_2$ antagonist avoided (as it needs acid for activation)
- Dose: 1 gm 1 Hr before meals
- ADRs: Constipation, hypophosphatemia
Misoprostol

- PGE$_1$ analogue
- Modest acid inhibition
- Stimulate mucus & bicarbonate secretion
- Enhance mucosal blood flow
- Approved for prevention of NSAID induced ulcer
- Diarrhoea & cramping abd. pain – 20 %
- Not so popular as other therapies are more effective & better tolerated
- Doses: 200 ug 4 times a day (Misoprostol)
Now answer this question

- A pregnant lady (first trimester) comes to you with peptic ulcer disease. Which drug will you prescribe for her?
Answer:

Antacids or Sucralfate

Explanation;

H₂ antagonists cross placenta and are also secreted in breast milk. Safety of Proton pump inhibitors not established in pregnancy. Misoprostol causes abortion.
Can you identify these people?

Nobel prize Medicine – 2005

Discovery of H.pylori & its role in ulcer

Barry J Marshall

J. Robin Warren
Eradication of H. pylori
Triple Therapy

- The BEST among all the Triple therapy regimen is Omeprazole / Lansoprazole - 20 / 30 mg bd
- Clarithromycin - 500 mg bd
- Amoxycillin / Metronidazole - 1gm / 500 mg bd

- Given for 14 days followed by P.P.I for 4 – 6 weeks
- Short regimens for 7 – 10 days not very effective
Quadruple Therapy

- Given when Triple Therapy fails

- Omeprazole / Lansoprazole - 20 / 30 mg bd
- Bismuth subsalycilate - 2 tabs qid
- Metronidazole - 250 mg qid
- Tetracycline - 500 mg qid
Drugs causing peptic ulcer

- Non Steroidal Anti Inflammatory Drugs (NSAIDs)
- Glucocorticoids
- Cytotoxic agents
Stress induced ulceration after head trauma

stress induced ulceration after severe burns
A patient comes to your clinic at midnight complaining of heart burn. You want to relieve his pain immediately. What drug will you choose?
Answer is

Antacids

- Explanation:
  Antacids neutralize the already secreted acid in the stomach. All other drugs act by stopping acid secretion and so may not relieve symptoms at least for 45 min.