Contents

• Physiology of Gastric acid secretion
• An introduction to Peptic Ulcer Disease
• An outline on the Drugs used in such disorders
• Pharmacokinetics and Pharmacodynamics of important groups of Drugs
• Clinical pharmacology of Peptic Ulcer Disease
Physiology of Gastric Secretion

- Food
- CNS
- Vagus

• H₂ – cAMP
• M₃ & CCK₂ – IP₃-DAG
# Phases of gastric secretion

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

### Duodenal
- Age: 25-75 years
- Gnawing or burning upper abdomen pain relieved by food but reappears 1-3 hrs after meals
- Worse pain when stomach empty
- Bleeding occurs with deep erosion
  - Hematemesis
  - Melena

### Gastric
- Age: 55-65 years
- Relieved by food but pain may persist even after eating
- Anorexia, wt loss, vomiting
- Infrequent or absent remissions
- Small % become cancerous
- Severe ulcers may erode through stomach wall
Gastroesophageal Reflux Disease (GERD)

- Common and GI motility disorder
- Acidity of Gastric contents – most common factor
- Acid contents reflux back into esophagus
- Intense burning, sometimes belching
- Can lead to esophagitis, esophageal ulcers, and strictures
  - Barrett’s esophagus
- Commonly associated with obesity
- Improves with lifestyle management
Why Ulceration Occurs?

• High [H+] in the gastric lumen
• Require defense mechanisms to protect oesophagus and stomach
• Oesophagus – LES
• Stomach: a number of mechanisms
  – Mucus secretion: slows ion diffusion
  – Prostaglandins: I₂ and E₂ (alcohol, aspirin, and other drugs)
  – Bicarbonate ions
  – High Blood Flow (nitric oxide)
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
What may contribute imbalance?

- **Helicobacter pylori**
- NSAIDs
- Ethanol
- Tobacco
- Severe physiologic stress (Burns, CNS trauma, Surgery, Severe medical illness)
- Steroids
H. pylori

- Gram (-) rod with flagella
- H pylori is most common cause of PUD
- Transmission route fecal-oral
- Secretes urease → convert urea to ammonia
- Produces alkaline environment enabling survival in stomach
- Almost all duodenal and 2/3 gastric ulcer pt’s infected with HP
- Considered class 1 carcinogen → gastric cancer
- Higher prevalence in Low SES
Who are they?

Barry J Marshall

Nobel Laureates of Medicine – 2005

J. Robin Warren

Discovery of H. pylori & its role in peptic ulcer
NSAIDS

Damage to the cytoprotective role of PGs – 
PGE$_2$ and PGI$_2$
Differentiating between H. pylori and NSAID-induced ulcer

Ulcers associated with H. pylori

- More often in duodenum
- Often superficial
- Less severe GI bleeding

Ulcers associated with NSAIDs

- More often in stomach
- Often deep
- More severe GI bleeding
- Sometimes asymptomatic
Drugs of Ulcer treatment

Parietal Cell
Proton Pump Inhibitor (PPI)

Acetylcholine  Gastrin  Histamine

Histamine $H_2$ receptor antagonists
Muscarnic $M_3$ receptor
Muscarinic antagonists

Acetylcholine
Gastrin
CCK$_2$ receptor

Histamine $H_2$ receptor
cAMP-dependent pathway
Ca$^{2+}$-dependent pathway

Parietal cell

H$^+$/K$^+$-ATPase

Acid (HCl)
Gastric gland lumen
Proton pump inhibitors

Cl$^-$

Omeprazole
H$^+$

Sulphenamide intermediate
Enzyme-inhibitor complex

Nature Reviews | Drug Discovery
Proglumide

ACh

PGE₂

Histamine

Gastrin

Adenyl cyclase

\[ _+ \]

ATP

cAMP

Protein Kinase (Activated)

Ca²⁺

PGE receptor

\(+\)

\(M_3\)

Gastrin receptor

\(+\)

Proton pump

K⁺

H⁺

Gastric acid

Parietal cell

Lumen of stomach

Omeprazole

Ranitidine

Misoprostol

Proglumide

Antacid
Peptic Ulcers

Therapy Purpose

Therapy is directed at enhancing host defense or eliminating aggressive factors; i.e., H. pylori
Classification

1. Acid Neutralizing agents: (ANTACIDS)
   - Systemic: Sodium Bicarbonate and Sod. Citrate
   - Nonsystemic: Magnesium hydroxide, Mag. Treisilicate, Aluminium hydroxide gel, Magaldrate and calcium carbonate

2. Reduction in Gastric acid secretion:
   - H2 antihistamines: Cimetidine, Ranitidine, Famotidine, Nizatidine and Roxatidine
   - Proton pump inhibitors: Omeprazole, Lansoprazole Pantoprazole, Rabeprazole and Esomeprazole
   - Anticholinergics: Pirenzepine, Propantheline and Oxyphenonium
   - Prostaglandin analogue: Misoprostol
Classification – contd.

3. Ulcer protectives: Sucralfate, Colloidal Bismuth sudcitate

4. Anti-H. pylori Drugs: Amoxicillin, Clarithromycin, metronidazole, tinidazole and tetracycline
Antacids

- Weak bases that neutralize acid
- Also inhibit formation of pepsin
  (As pepsinogen converted to pepsin at acidic pH)

**Acid Neutralizing Capacity:**
- Potency of Antacids
- Expressed in terms of Number of mEq of 1N HCl that are brought down to pH 3.5 in 15 minutes by unit dose of a preparation (1 gm)
Antacids - The Oldest Remedy

- **Sodium Bicarbonate:**
  - Potent neutralizing capacity and acts instantly
  - ANC: 1 gm = 12 mEq

- **NOT USED ANYMORE FOR ITS DEMERITS:**
  - Systemic alkalosis
  - Distension, discomfort and belching – $\text{CO}_2 \uparrow$
  - Rebound acidity
  - Sodium overload
Antacids

• **Present day antacids:**
  - Aluminium Hydroxide (ANC 1-2.5mEq/g)
  - Magnesium Hydroxide (ANC 30 mEq) – milk of magnesia
  - Magnesium trisilicate (ANC 1mEq/g)

• Duration of action: 30 min when taken in empty stomach and 2 hrs when taken after a meal

• **Side effects:**
  - Aluminium antacids – constipation (As they relax gastric smooth muscle & delay gastric emptying) – also hypophosphatemia and osteomalacia
  - Mg2+ antacids – Osmotic diarrhoea

• In renal failure Al3+ antacid – Aluminium toxicity & Encephalopathy
  (Magaldrate – hydrated hydroxy magnesium aluminate)
Antacids – contd.

- **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
Therapeutic Questions

• Is it rational to combine Aluminium hydroxide and magnesium hydroxide in antacid preparations?

• How to avoid formation of insoluble complexes of drugs by antacids, that are not absorbed?
Answers (!)

• Interactions can be avoided by taking antacids 2 hrs before or after ingestion of other drugs
• 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 – diarrhoea )
The Reality

- **Not part of Physician prescribed regimen – frequency of dosing and rebound acidity**
- Over the counter (OTC) drug for symptomatic relief of dyspepsia
- May only be prescribed for very short term:
  - Non-ulcer dyspepsia and minor episodes of heart burn
  - As adjuvant in GERD – quick relieve
Sucralfate – ulcer protective

- Salt of sucrose complexed to sulfated aluminium hydroxide (basic aluminium salt)
- MOA:
  - In acidic pH polymerises to viscous gel that adheres to ulcer crater - more on duodenal ulcer
  - Precipitates protein on surface proteins and acts as physical barrier
  - Dietary proteins get deposited on this layer forming another coat
  - Delays gastric emptying and causes gastric PG synthesis – protective action
Sucralfate – contd.

- Taken on empty stomach 1 hr. before meals
- Concurrent antacids, $H_2$ antagonist avoided (as it needs acid for activation)
- Uses:
  - NSAID induced ulcers
  - Patients with continued smoking
  - ICU
  - Topically – burn, bedsore ulcers, excoriated skins
- Dose: 1 gm 1 Hr before meals
- ADRs: Constipation, hypophosphatemia
Chemical reactions of antacids with HCl in the stomach

- \( \text{NaHCO}_3 + \text{HCL} \rightarrow \text{NaCl} + \text{H}_2\text{O} + \text{CO}_2 \)
- \( \text{CaCO}_3 + 2 \text{HCl} \rightarrow \text{CaCl}_2 + \text{H}_2\text{O} + \text{CO}_2 \)
- \( \text{Al(OH)}_3 + 3 \text{HCl} \rightarrow \text{AlCl}_3 + 3 \text{H}_2\text{O} \)
- \( \text{Mg(OH)}_2 + 2 \text{HCl} \rightarrow \text{MgCl}_2 + 2 \text{H}_2\text{O} \)
Antacids

Capsules & Tablets:

- Powders
- Chewable tablets
- Suspensions
- Effervescent granules and tablets
H₂ Antagonists

- **Cimetidine, Ranitidine, Famotidine, Roxatidine, Nizatidine and**
- **MOA:**
  - Reversible competitive inhibitors of H₂ receptor
  - Highly selective, no action on H₁ or H₃ receptors
  - All phases of gastric acid secretion
  - 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, acetylcholine and histamine)
  - Volume of pepsin content and IF are also reduced
  - Volume reduced by 60 – 70% - anti ulcerogenic effect
  - No effect on motility
H$_2$ antagonists

• Kinetics:
  – All drugs are absorbed orally adequately
  – Bioavailability upto 80 %
  – Absorption is not interfered by presence of food
  – Can cross placental barrier and reaches milk
  – Poor CNS penetration
  – $2/3^{rd}$ of the drugs are excreted unchanged in bile and urine

• Preparations: available as tablets, injections
H₂ antagonists - ADRs

• Extremely safe drugs and well tolerated
• Main ADRs are related to Cimetidine:
  – **Antiandrogenic** effects
  – Increases **prolactin** secretion and inhibits degradation of **estradiol** by liver
  – Cytochrome P450 inhibition – theophylline, metronidazole, phenytoin, imipramine etc.
  – Antacids

• Others:
  – Headache, dizziness, bowel upset, dry mouth
  – Bolus IV – release histamine – bradycardia, arrhythmia, cardiac arrest
  – Elderly - precaution
## Comparison of H₂ antagonists

<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</td>
<td>6</td>
<td>8</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>action (hrs)</td>
<td></td>
<td></td>
<td></td>
<td></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>
</tbody>
</table>

Antiandrogenic effect, prolactin secretion and gynecomastia
**H₂ antagonists - Uses**

**Promote the healing of gastric and duodenal ulcers**

- Duodenal ulcer – 70 to 90%
- Gastric Ulcer – 50 to 75% (NSAID ulcers))
- Stress ulcer and gastritis
- GERD
- Zollinger-Ellison syndrome
- Prophylaxis of aspiration pneumonia
- Urticaria

**Doses:**

- 300 mg/40 mg/150 mg at bed time of R, F, Rox respectively for healing
- Maintenance: 150/20/150 mg BD of R, F, Rox
### H₂ blockers Tablets in Peptic ulcer

<table>
<thead>
<tr>
<th></th>
<th>800mg bedtime /400mgBd</th>
<th>400mg bedtime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimetidine</td>
<td>800mg bedtime /400mgBd</td>
<td>400mg bedtime</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>300 mg bedtime/150mg BD</td>
<td>150 mg bedtime</td>
</tr>
<tr>
<td>Famotidine</td>
<td>40 mg bedtime</td>
<td>20 mg bedtime</td>
</tr>
<tr>
<td>Roxatidine</td>
<td>150 mg bedtime</td>
<td>75 mg bedtime</td>
</tr>
</tbody>
</table>
Your friend wants to take a H$_2$ antagonist before he takes alcohol to avoid gastric irritation. He consults you. Which H$_2$ antagonist will you ask him to take?

Ranitidine/Famotidine/Roxatidine/Tiznidine?
H$_2$ antagonists – contd.

• Answer:
  
  Famotidine

• Explanation:

All H$_2$ antagonist except famotidine inhibit gastric first pass metabolism of ethanol and increase its bioavailability.
Proton Pump Inhibitors

- Most effective drugs in antiulcer therapy
- **Prodrugs** requiring activation in acid environment
- Block enzymes responsible for secreting HCl - binds irreversibly to H+K+ATPase
- Prototype: **Omeprazole** (Prilosec)
- Examples:
  - Lansoprazole
  - Pantoprazole
  - Rabeprazole
  - Esomeprazole
Omeprazole - MOA

- Substituted Benzimidazole derivative
- It's a Prodrug
- Diffuses into G. canaliculi = accumulation pH < 5 (proton catalyzed) = tetracyclic sulfenamide + sulphenic acid
- Covalent binding with sulfhydryl cysteines of H⁺K⁺ ATPase
- Irreversible inactivation of the pump molecule (The charged forms cannot diffuse back across the canaliculi)
- Acid suppressants regardless of stimulating factors
- Also inhibits gastric mucosal carbonic anhydrase
Pharmacokinetics - PPI

- Oral forms are prepared as acid resistant formulations that release the drug in the intestine (because they are degraded in acid media)
- After absorption, they are distributed by blood to **parietal cell canaliculi**
- They irreversibly inactivate the proton pump molecule – but half life is very short and only 1-2 Hrs
- **Still action persists for 24 Hrs to 48 hrs** after a single dose – irreversible inhibition of PPI and new PP synthesis takes time (24 to 48 hour suppression of acid secretion, despite the much shorter plasma half-lives of the parent compounds)
- Plaque state is attained after 4-5 days of dosing
- Action lasts for 4-5 days even after stoppage of the drug
Question

• Half life of proton pump inhibitors is 1.5 hours only and these drugs are generally given once daily. How this can be justified?

• Answer:
  – P.P.I - Irreversible inhibitors of H+K+ATPase
    (Hit and run drugs)
Pharmacokinetics - PPI

- **Given on an empty stomach because food affects absorption**
- They should be given 30 minutes to 1 hour before food intake because an acidic pH in the parietal cell acid canaliculi is required for drug activation, and food stimulates acid production
- Concomitant use of other antisecretory drugs - H2 receptor antagonists – reduces action
- Highly protein bound and rapidly metabolized by the liver by CYP2C19 and CYP3A4 – dose reduction necessary in severe hepatic failure
- Excreted in Kidneys minimally (no dose reduction needed in renal failure and elderly)
Adverse Effects

- The most common are GIT troubles in the form of nausea, abdominal pain, constipation, flatulence, and diarrhea
- Subacute myopathy, arthralgias, headaches, and skin rashes
- Prolonged use:
  - Gynaecomastia, erectile dysfunction
  - Leucopenia and hepatic dysfunction
  - Vitamin B12 deficiency
  - Hypergastrinemia which may predispose to rebound hypersecretion of gastric acid upon discontinuation of therapy and may promote the growth of gastrointestinal tumors (carcinoid tumors)
PPI – contd.

• Drug Interaction:
  – Inhibits metabolism of Warfarin, Diazepam

• Therapeutic uses:
  1. Gastroesophageal reflux disease (GERD)
  2. Peptic Ulcer - Gastric and duodenal ulcers
  3. Bleeding peptic Ulcer
  4. Zollinger ellison Syndrome
  5. Prevention of recurrence of nonsteroidal antiinflammatory drug (NSAID) - associated gastric ulcers in patients who continue NSAID use.
  6. Reducing the risk of duodenal ulcer recurrence associated with H. pylori infections
  7. Aspiration Pneumonia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bioavailability</th>
<th>Half-Life (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>40–65%</td>
<td>0.5–1</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>50–89%</td>
<td>1.2</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>80–90%</td>
<td>1.5</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>77%</td>
<td>1.9</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>52%</td>
<td>0.7–2.0</td>
</tr>
</tbody>
</table>
PPI – Dosage schedule

- Omeprazole 20 mg o.d.
- Lansoprazole 30 mg o.d.
- Pantoprazole 40 mg o.d.
- Rabeprazole 20 mg o.d.
- Esomeprazole 20 - 40 mg o.d.
Muscarinic antagonists

Atropine:
- Block the M1 class receptors
- Reduce acid production
- Abolish gastrointestinal spasm

Pirenzepine and Telenzepine

Mechanism of action:
- Reduce meal stimulated HCl secretion by reversible blockade of muscarinic (M1) receptors on the cell bodies of the intramural cholinergic ganglia
  (receptors on parietal cells are M3).

- Unpopular as a first choice because of high incidence of anticholinergic side effects (dry mouth and blurred vision)
Prostaglandin analogues

- Inhibit gastric acid secretion
- Exhibit ‘cytoprotective’ activity
- Enhance local production of mucus or bicarbonate
- Promote local cell regeneration
- Help to maintain mucosal blood
Prostaglandin analogues - Misoprostol

• **Actions:**
  - Inhibit histamine-stimulated gastric acid secretion
  - Stimulation of mucin and bicarbonate secretion
  - Increase mucosal blood flow
  
  *(Reinforcing of mucous layer buffered by HCO3 secretion from epithelial cells)*

• **Therapeutic uses:**
  Prevent ion of NSAID-induced mucosal injury
  *(rarely used because it needs frequent administration – 4 times daily)*
**Misoprostol**

- **Doses:** 200 mcg 4 times a day (Misoprost)
- **ADRs:**
  - Diarrhoea and abdominal cramps
  - Uterine bleeding
  - Abortion
  - Exacerbations of inflammatory bowel disease and should be avoided in patients with this disorder

**Contraindications:**
1. Inflammatory bowel disease
2. Pregnancy (may cause abortion)
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.
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
Some other Triple Therapy Regimens are:

- Bismuth subsalicylate – 2 tab qid
- Metronidazole - 250 mg qid
- Tetracycline - 500 mg qid

- Ranitidine Bismuth citrate - 400 mg bd
- Tetracycline - 500 mg bd
- Clarithromycin / Metronidazole - 500 mg bd
Bismuth subsalicylate

Pharmacological actions:

• Undergoes rapid dissolution in the stomach into bismuth and salicylates
• Salicylates are absorbed
• Bismuth coats ulcers and erosions protecting them from acid and pepsin and increases prostaglandin and bicarbonate production

Uses:

• Treatment of dyspepsia and acute diarrhoea
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.
Additional

Drugs causing peptic ulcer:
• Non Steroidal Anti Inflammatory Drugs (NSAIDs)
• Glucocorticoids
• Cytotoxic agents

Stress induced ulceration after head trauma - Cushing’s ulcer
Stress induced ulceration after severe burns - Curling’s ulcer
H2 Receptor Antagonists

- In stomach at all stages decreases formation of HCl by selective blocking of H2 receptors – therapeutic effect after 4 weeks – 60–80% efficiency, after 8 weeks even 90%, 10–15% resistance

Ranitidine, Famotidine /more effective/, Nizatidine: /1–2x daily/ – good pharmacokinetic /p.o. absorption, metabolism in liver/ and safety profile, good tolerance – long-term maintenance therapy after uncomplicated peptic ulcer healing and treatment of some forms of gastric dyspepsias