

Drugs for Peptic Ulcer Disease

Dr Pradeep

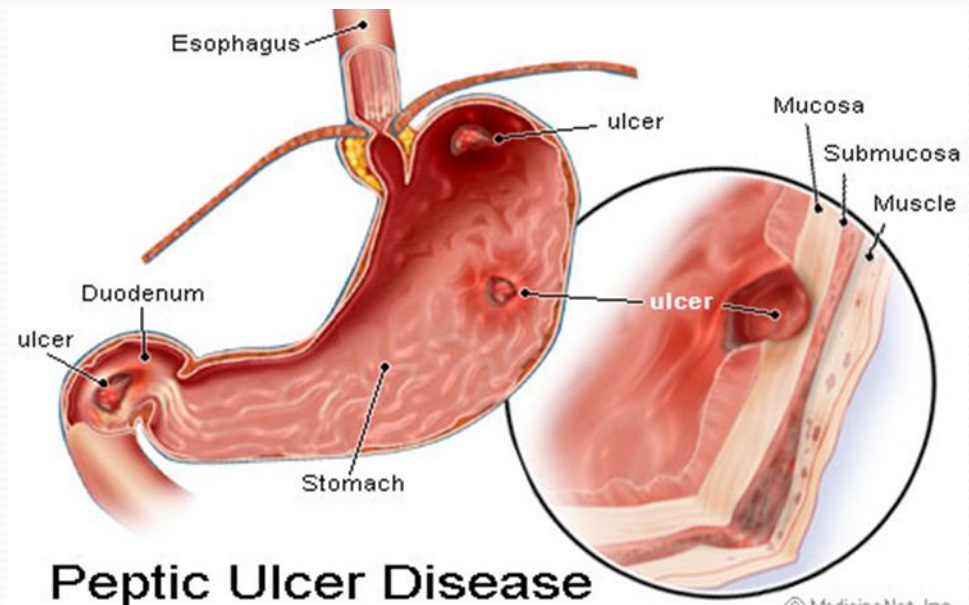
Department of Pharmacology

MGM Medical & Dental Collge, NaviMumbai

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Background

- Acid peptic diseases include gastro esophageal reflux, **peptic ulcer (gastric & duodenal)** and stress related mucosal injury.
- Peptic ulcer disease = Mucosal break/defect in the gastrointestinal tract (gastric or duodenal) exposed to acid and pepsin secretion



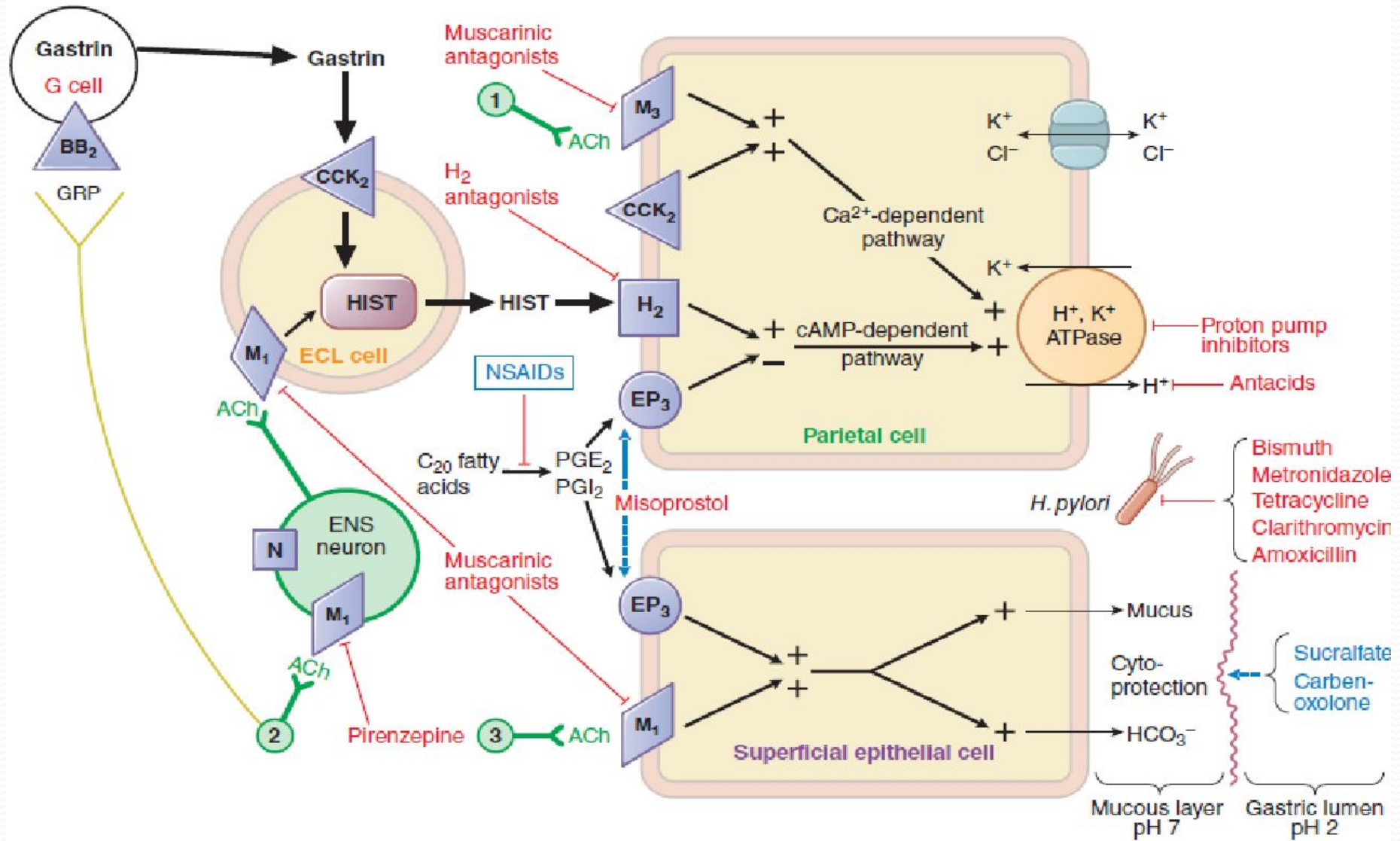
Etiology of peptic ulcer

- The etiology of peptic ulcer is not clearly known.
- It results probably due to an **imbalance between the aggressive** (acid, pepsin, bile and H. pylori)
And
- **the defensive** (gastric mucus and bicarbonate secretion, prostaglandins, nitric oxide, innate resistance of the mucosal cells) factors.

Etiology of peptic ulcer

- Erosion or Mucosal ulceration occurs when the aggressive factors (**Acid Pepsin**)
Overwhelm
- the defensive factors (**mucus, bicarbonate, PGS, blood flow and the process of regeneration after cellular injury**)
- Also a subset of peptic ulcer is caused by the infection with *Helicobacter pylori* (70%) or by non-steroidal anti inflammatory drugs (aspirin like drugs).

Regulation of acid secretion and Pharmacological drug targets



Drugs Used in Peptic Ulcer

● Drugs are broadly divided into following groups.

1. Neutralization of gastric acid
2. Reduction of gastric acid secretion
3. Ulcer protective
4. Anti-H. pylori drugs

Neutralization of gastric acid :

- Antacids : These are basic substances which neutralize gastric acid and raise pH (alkaline) of gastric contents
1. Systemic: Sodium Bicarbonate and Sodium Citrate
 2. **Nonsystemic: Magnesium hydroxide, Mag. Trisilicate, Aluminium hydroxide gel, Magaldrate**

Antacids

- Antacids are now employed only for intercurrent Symptomatic pain relief and acidity
- **Present day antacids :**
 - Aluminium Hydroxide (1-2.5mEq/g)
 - Magnesium Hydroxide (30 mEq) – milk of magnesia
 - Magnesium trisilicate (1mEq/g)
- Duration of action : 30 min when taken in empty stomach and 2 hrs. when taken after a meal

Antacids combination

- A combination of two or more antacids is frequently used. May be superior to single agent & provide following benefits :
(E.g. Aluminium Hydroxide and Magnesium Hydroxide)
- (a) Fast (Magnesium salts) and slow (Aluminium salts) acting components yield prompt as well as sustained effect.
- (b) Magnesium salts are laxative, while Aluminium . salts are constipating: combination may annul each other's action and bowel movement may be least affected.
- (c) Gastric emptying is least affected; while Aluminium . salts tend to delay it, Magnesium salts tend to hasten it.
- (d) Dose of individual components is reduced; systemic toxicity (dependent on fraction absorption) is minimized

Reduction of gastric acid secretion

- **a) H₂ antihistamines/H₂ blockers:** Cimetidine, **Ranitidine**, **Famotidine**, Roxatidine
- **(b) Proton pump inhibitors:** **Omeprazole**, Lansoprazole, **Pantoprazole**, **Rabeprazole**, Esomeprazole
- **(c) Anticholinergics:** **Pirenzepine**, Propantheline, Oxyphenonium
- **(d) Prostaglandin analogue:** **Misoprostol**

H2 antihistamines/H2 blockers

- H2 antihistamines/H2 blockers: Cimetidine, **Ranitidine**, **Famotidine**, Roxatidine
- **Mechanism of action :**
- H2 antagonists /blockers exhibit competitive inhibition at the parietal cell H2 (**histamine**) receptors and suppress basal and meal stimulated acid secretion in a linear dose dependent fashion.
- **They block histamine-induced gastric secretion >> decreases acid secretion**

Ranitidine vs Cimetidine

- Ranitidine- A nonimidazole (has a furan ring) H₂ blocker, has several desirable features compared to cimetidine:
- About 5 times more potent than cimetidine
- Though its pharmacokinetic profile and t-half of 2-3 hr is similar to cimetidine, a longer duration of action with greater 24 hr acid suppression because of higher potency.
- No antiandrogenic action, no effect on male sexualfunction or gynaecomastia. •
- Lesser permeability into brain: lower risk to cause CNS effects.
- Does not significantly inhibit hepatic metabolism of other drugs; drug interactions mostly have no clinical relevance.
- Overall incidence of side effects is lower

H2 blockers – therapeutic uses

H2 blockers produce rapid and marked pain relief (within 2-3 days); 85% ulcers heal at 4 weeks and 70-95% ulcers at 8 weeks

- **Hyperacidity**
- **Duodenal ulcer**
- **Gastric ulcer**
- **Stress ulcers and gastritis**
- **Prophylaxis of aspiration pneumonia**

- Zollinger-Ellison syndrome
- Gastroesophageal reflux disease (GERD)

H2 blockers – adverse effects

Generally safe drugs and well tolerated

Diarrhoea, headache, myalgia, constipation, fatigue, confusion

Main ADRs are related to Cimetidine:

- Antiandrogenic effects, gynacomastia
- Increases prolactin secretion and inhibits degradation of estradiol by liver
- Drug interaction : Cytochrome P450 inhibition – theophylline, metronidazole, phenytoin

Proton pump inhibitors (PPI):

- **Proton pump inhibitors: Omeprazole, Lansoprazole, Pantoprazole, Rabeprazole, Esomeprazole**
- Most effective drugs in antiulcer therapy
- Prodrugs requiring activation in acid environment
- **Blocks the final common step in gastric acid secretion**
- **Blocks the enzymes responsible for secreting HCl - binds irreversibly to H⁺K⁺ATPase in parietal cells**
- Prototype: Omeprazole

PPI: Mechanism of action

- **Proton pump inhibitors (PPI) :** Omeprazole
- **Mechanism of action :**
- Prodrug Omeprazole -Produce active reactive thiophilic sulfonamide cation reacts with H^+/K^+ ATPase enzyme by covalent disulfide linkage and irreversibly inactivate /inhibits the enzyme.
- It inhibits the acid secretion for 24 hours. 18 hours are required to synthesize the new H^+/K^+ ATPase

PPI– therapeutic uses

Proton pump inhibitors (PPI): Ideal Anti-ulcer drugs

- Highly efficacious
- Short $t_{1/2}$
- Well concentrated
- H^+/K^+ ATPase exist only in parietal cell.
- Long duration of action
- Safe
- Well tolerated
- Better compliance

PPI– therapeutic uses

Proton pump inhibitors (PPI): uses

- Gastroesophageal reflux disease (GERD) along with prokinetic drugs
- Peptic Ulcer - Gastric and duodenal ulcers
- Bleeding peptic Ulcer
- Zollinger ellison Syndrome
- Prevention of recurrence of nonsteroidal antiinflammatory drug (NSAID) - associated gastric ulcers in patients who continue NSAID use.
- Reducing the risk of duodenal ulcer recurrence associated with H. pylori infections
- Aspiration Pneumonia

PPI: 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)

Anticholinergics

- **Anticholinergics: Pirenzepine, Propantheline, Oxyphenonium**
- Mechanism of action of Reduces gastric acid secretion & delay gastric emptying.
- Pirenzepine: M1(muscarinic) receptor antagonist. It inhibits muscarinic mediated gastric secretion
- The more likely site is intramural plexuses and ganglionic cells rather than the parietal cells themselves.
- Adverse effects - typical atropine like side effects.
- Currently not preferred, as H2 blockers and PPI are more efficacious and safe

Prostaglandin analogue

- **Prostaglandin (PG)analogue: Misoprostol**
- PGE2 and PGI2 are produced in the gastric mucosa and appear to serve a protective role by inhibiting acid secretion and promoting mucus and bicarbonate secretion.
- In addition inhibit gastrin production, increase mucosal blood flow and probably have an ill-defined "cytoprotective" action.
- **thus prostaglandin analogues are useful**

Prostaglandin analogue

- **Prostaglandin (PG)analogue: Misoprostol**

- **Therapeutic uses:**

Prevent ion and treatment of NSAID-induced mucosal injury/
NSAID-induced ulcers and associated blood loss

Adverse effects

- Major problems in the use of misoprostol are- diarrhoea, abdominal cramps, uterine bleeding, abortion, and need for multiple daily doses.
- Should not be administered during pregnancy or women of child bearing potential

Ulcer protective

- **Sucralfate, Colloidal bismuth subcitrate (CBS)**

Sucralfate

Pharmacological actions:

- It is a basic aluminium salt of sulfated sucrose
- Sucralfate polymerizes at $\text{pH} < 4$ by cross linking of molecules, assuming a sticky gel-like consistency It preferentially and strongly adheres to ulcer base, especially duodenal ulcer; to remain there for - 6 hours.
- It precipitates surface proteins at ulcer base and acts as a physical barrier preventing acid, pepsin and bile from coming in contact with the ulcer base.

Ulcer protective

Colloidal bismuth subcitrate (CBS)

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

Anti-*H. pylori* drugs

Role of *H. Pylori* infection in peptic ulcer disease

H. pylori is a gram negative bacillus uniquely adapted to survival in the hostile environment of stomach. It attaches to the surface epithelium beneath the mucus, has high urease activity produces ammonia which maintains a neutral microenvironment around the bacteria, and promotes back diffusion of H^+ ions.

- It has been found as a commensal in 20-70% normal individuals, and is now accepted as an important contributor to the causation of chronic gastritis, dyspepsia, peptic ulcer, gastric lymphoma and gastric carcinoma.

Anti-H.pylori drugs- Triple Therapy

The Antimicrobials that have been found clinically effective against H. pylori (Anti-H.pylori) and recommended for Triple-therapy regimen is:

- 1 Omeprazole / Lansoprazole** - 20 / 30 mg bd
- 2 Clarithromycin** - 500 mg bd
- 3 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

Triple Therapy – cont

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

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

Goals of anti-ulcer therapy

Goals of antiulcer therapy are:

- (i) Relief of pain
- (ii) Ulcer healing
- (iii) Prevention of complications
- (iv) Prevention of relapse

Thank you

Please refer standard textbook (latest version)
of medical / dental pharmacology for details

- KD Tripathi
- Satoshkar and Bandarkar