

## Pharmacotherapy of Peptic ulcer

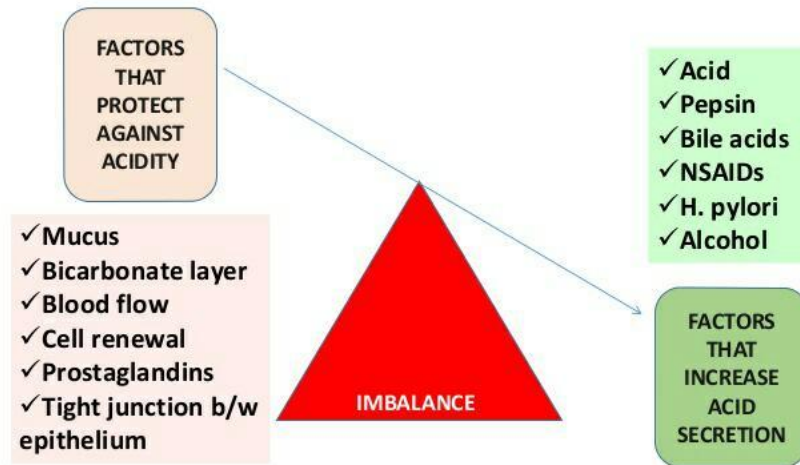
- Objectives of this topic –

1. Regulation of HCL secretion.
2. Classification of various drugs used in the treatment of peptic ulcers.
3. Mechanism of action, uses, kinetics and ADRs of various drugs.
4. Drugs for eradication of H.pylori.

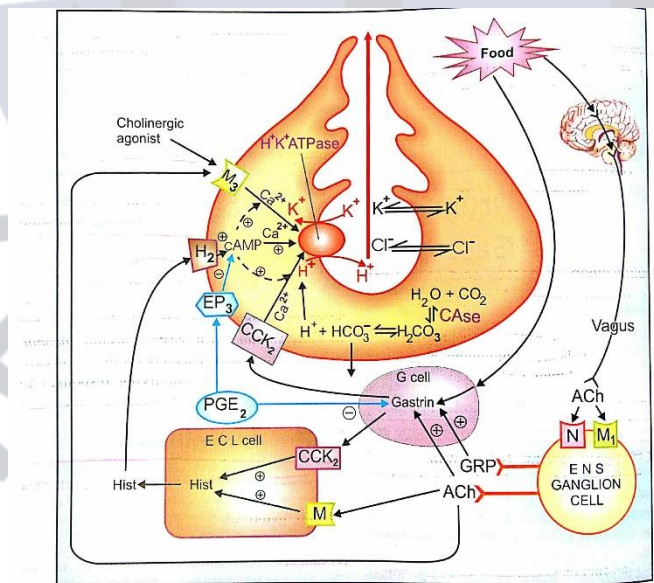
- Why does peptic ulcer occur??

Peptic ulcer results due to imbalance between the aggressive and defensive factors.

## PEPTIC ULCER DISEASE



### • Normal regulation of gastric HCL secretion-



**Figure 46.1: Secretion of HCl by gastric parietal cell and its regulation**  
 C. Ase.—Carbonic anhydrase; Hist.—Histamine; ACh.—Acetylcholine;  $CCK_2$ —Gastrin cholecystokinin receptor; M.—Muscarinic receptor; N.—Nicotinic receptor;  $H_2$ —Histamine  $H_2$  receptor;  $EP_3$ —Prostaglandin receptor; ENS—Enteric nervous system; ECL cell—Enterochromaffin-like cell; GRP—Gastrin releasing peptide; + Stimulation; – Inhibition.

- Classification of drugs used. :

Broadly the drugs are classified as follows –

1. **Reduction of gastric acid secretion**

- a) *H2 antihistamines :*

Cimetidine, Ranitidine, Ranitidine, Roxatidine.

- b) *Proton pump inhibitors:*

Omeprazole, Esomeprazole, Lansoprazole, Pantaprazole.

- c) *Anticholinergic drugs:*

Pirenzepine, Propantheline, Oxyphenonium.

- d) *Prostaglandin analogue:*

Misoprostol.

2. **Neutralization of gastric acid (antacids)**

- a) *Systemic*

Sodium bicarbonate, Sodium citrate.

- b) *Nonsystemic*

Magnesium hydroxide, Magnesium trisilicate , Aluminium hydroxide, calcium carbonate.

3. **Ulcer protectives**

Sucralfate, Colloidal bismuth subcitrate.

4. **Anti H.pylori drugs**

Amoxicillin, Clarithromycin, Metronidazole, Tinidazole, Tetracycline.

Difficult to remember, right???

Here's an easy way!!

Remember as **“PEPTIC “**

**P – Proton pump inhibitors**

**E** – PGE2 and PGI2 analogues

**P** – Pylori eradicators

**T** – Tinidine, like cimetidine (H2 antihistamines)

**I** – Intestinal antacids

**C** – Anti Cholinergic

& Colloidal bismuth sulfate (ulcer protectives)

## 1] H2 antagonists –

- These drugs competitively inhibit H2 receptors in parietal cells, thus inhibiting acid secretion.
- Ach & gastrin also act partly by causing release of histamine, so acid secreting capacity of these agents is also decreased.
- All phases of gastric acid secretion are suppressed.
- These drugs are more effective for reducing the basal (nocturnal) acid secretion than stimulated acid secretion.
- Normal Vit. B12 absorption is not interfered.

- **Cimetidine:**

- Was the first H2 blocker discovered.
- It crosses the placenta & reaches milk, penetration in brain is poor.
- It inhibits binding of dihydrotestosterone to androgen receptors – impotence in males.
- It inhibits metabolism of estradiol & increases the serum prolactin levels, thus can cause gynaecomastia in males.
- It is a potent inhibitor of many CYP enzymes, can cause decrease in concentration of warfarin, theophylline, etc.
- Among the H2 blockers, it is the least potent.
- Pharmacokinetics –  
Adequately absorbed orally, bioavailability – 60-80%  
Half Life – 2-3 hour

- **Ranitidine –**

Advantages over cimetidine –

- 5 times more potent
- No antiandrogenic activity
- Lesser permeability into brain
- Less inhibition of CYP enzymes
- Overall side effects are low.

**Uses :-**

1. Duodenal ulcer
2. Gastric ulcer
3. Stress ulcer & gastritis
4. Zollinger- Ellison syndrome
5. GERD

- Famotidine is the most potent H<sub>2</sub> blocker.
- Loxatidine is a non competitive inhibitor of H<sub>2</sub> receptors.
- Nizatidine also possess anti-AChE activity
- Nizatidine has negligible first pass metabolism ( 100% bioavailability)

## **2] Proton pump inhibitors :-**

- These are prodrugs (active moiety is sulfenamide)
- Act irreversibly by inhibiting H<sup>+</sup> K<sup>+</sup> ATPase in gastric parietal cells.

- These drugs are weak bases & can be destroyed by gastric acid. To protect them from gastric acid, they are given as enteric coated tablets.

- These can inhibit both basal acid output as well as meal stimulated acid output.

- **Omeprazole -**

- Prototype member.
- The imp pharmacological action is dose dependent suppression of gastric acid secretion, without anticholinergic or H<sub>2</sub> blocking action .
- Omeprazole is inactive at neutral pH, but at pH <5 it rearranges to two charged cationic forms that react covalently with SH groups of H-K ATPase enzyme and inactivates it indirectly.

- **Pharmacokinetics –**

- Administered orally.
- Bioavailability of all PPIs is reduced by food, should be taken in empty stomach followed one hour later by a meal to activate the proton pump
- Plasma half life –1 hr
- Even with short half life they can inhibit acid secretion for more than 24 hours – **Hit and run drugs.**
- All PPIs are substrates of CYP2C19 and CYP3A4 except, Rabeprazol. PPIs also inhibit these enzymes and cause drug interactions.

- **Uses –**

1. **Peptic ulcer** - they are used in peptic ulcers due to any etiology.
2. **Bleeding peptic ulcer**
3. **Stress ulcer**
4. **GERD**
5. **ZE syndrome**

- **Adverse effects–**

- PPIs are quite safe drugs.
- Nausea, headache, diarrhoea, abdominal pain , dizziness are the side effects.
- Are safe during pregnancy.

**Long term use of PPIs is associated with –**

- Reduced absorption of vit. B12
- Increased risk of hip fractures
- Increased risk of enteric bacterial infections.

**Note :**

- Lanoprazol is most potent PPI
- Lanoprazol is safest PPI in pregnancy
- Rabeprazol is fastest acting PPI
- Rabeprazol has minimum inhibitory effect on CYP enzymes.

### 3] Prostaglandin analogues :-

- PGE<sub>2</sub> markedly reduces acid secretion in stomach.

It inhibits fasting as well as stimulated secretion of acid.

-The gastric pH rises upto 7.0

- PGI<sub>2</sub> also inhibits gastric secretion, but is less potent.

- They cause a increase in mucous and bicarbonate secretion as well as mucosal blood flow is increased.

- Thus PGs are antiulcerogenic.

PGs reinforce the mucous layer covering gastric acid & duodenal mucosa which is buffered by bicarbonate.

-Misoprostol is the most specific drug for treatment and prevention of NSAID induced peptic ulcer.

- Commonest side effects are diarrhoea and colicky abdominal pain.

#### 4] Anticholinergics :-

- Non selective anti-muscarinic drugs like propantheline can be used for decreasing gastric acidity.
- But, these drugs also increase the gastric emptying time, so there is prolonged exposure of ulcer bed to gastric acid.
- Also, other s/e like dry mouth, blurred vision, constipation are seen.
- Pirenzepine, telenzepine are selective M1 blockers & are preferred for peptic ulcer disease.

#### 5] Antacids :-

- These are weak bases which neutralize the gastric acid & raise pH of gastric contents.
- Their **major role** in peptic ulcer is to provide **relief from ulcer pain**.
- Antacids may be **systemic** (absorbed from GIT) or **local** (poorly absorbed).

- **Non systemic antacids-**

- These are insoluble basic compounds, react in stomach & form chloride salts.
- Aluminium hydroxide, magnesium hydroxide, magnesium trisilicate, magnesium carbonate are the drugs.
- **Slower but longer acting drugs.**
- Rebound acidity does not occur.
- Magnesium salts are fast acting, aluminium salts are slow acting.
- Aluminium causes constipation whereas magnesium causes diarrhoea.
- So, a combination of these drugs are used to minimise the impact on bowel.

- **Antacid combinations –**

1. Magnesium (fast acting) & aluminium (slow acting) provide a prompt and sustained action
2. Mag. salts are laxatives & alum. salts are constipating, so combination annul each other's actions.
3. Alum salts delay gastric emptying, while mag salts or calcium salts hasten it
4. Individual drug dosage is reduced – less systemic side effects.

## Systemic antacids-

- Sodium bicarbonate is rapidly acting systemic antacid.
- Not indicated for long term use because-

- It releases CO<sub>2</sub> that can cause belching & gastric distension (ulcer perforation may occur)
- Sodium chloride formed as a result of neutralization can be reabsorbed that can exacerbate fluid retention in CHF & hypertension.
- Systemic & urinary alkosis may occur
- Rebound hyperacidity.

- **Milk alkali syndrome :**

In past, large quantities of milk was prescribed with calcium salts for peptic ulcer. This regimen produced a syndrome characterized by headache, anorexia, weakness, abdominal discomfort, abnormal Ca deposits & renal stones.

## 6] Ulcer protectives :-

These drugs form a covering over the ulcer bed that prevents the exposure to gastric acid.

Sucralfate & colloidal bismuth sulfate are two important ulcer protectives

- **Sucralfate –**

- It is a aluminium salt of sulfated sucrose.
- At pH below 4, it's molecule polymerizes to form a sticky layer that covers the ulcer base & acts as a physical barrier to prevent acid exposure.
- Has no acid neutralizing action.
- Promotes healing of ulcer.
- It should not be given with antacids because it acts only in acidic medium.

- Most common side effect is constipation.
- Binds to phosphates and results in hypophosphatemia
- *Colloidal bismuth sulfate*—
  - Water soluble, not an antacid, but heals ulcer.
  - May increase gastric mucosal PGE<sub>2</sub>, mucous & HCO<sub>3</sub>
  - May detach and inhibit H pylori directly.
  - The regimen for CBS is 120 mg taken ½ hr before 3 major meals & at bedtime for 4-8 weeks.
  - Blackening of tongue, dentures and stools is an important ADR.

## 8] Anti H. pylori drugs –

- H. pylori is a gram negative bacillus adapted to the hostile environment of stomach.
- It is responsible for relapse of peptic ulcer disease.

**Antimicrobials used are -**

**Amoxicillin, Clarithromycin, tetracycline, and metronidazole.**

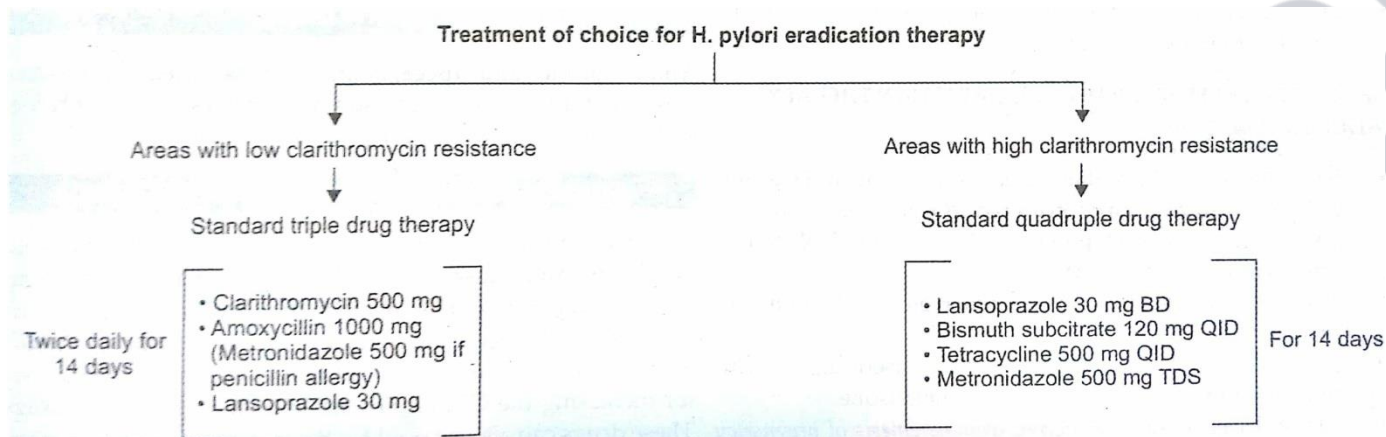
- Acid suppression by PPIs/H<sub>2</sub> blockers enhances the effectiveness of anti H. pylori antibiotics.
- A triple drug therapy regimen is used.

**Triple drug regimen –CAP**

**C – Clarithromycin**

**A – Amoxicillin**

**P – Proton pump inhibitor.**



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