

Pharmacology-III

UNIT-I

Drugs acting on gastro-intestinal tract ANTI-ULCER DRUGS

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Shaping Lives...
Empowering Communities...

Drugs acting on gastro- intestinal tract:



Drugs action GIT: To treat GI disorder:

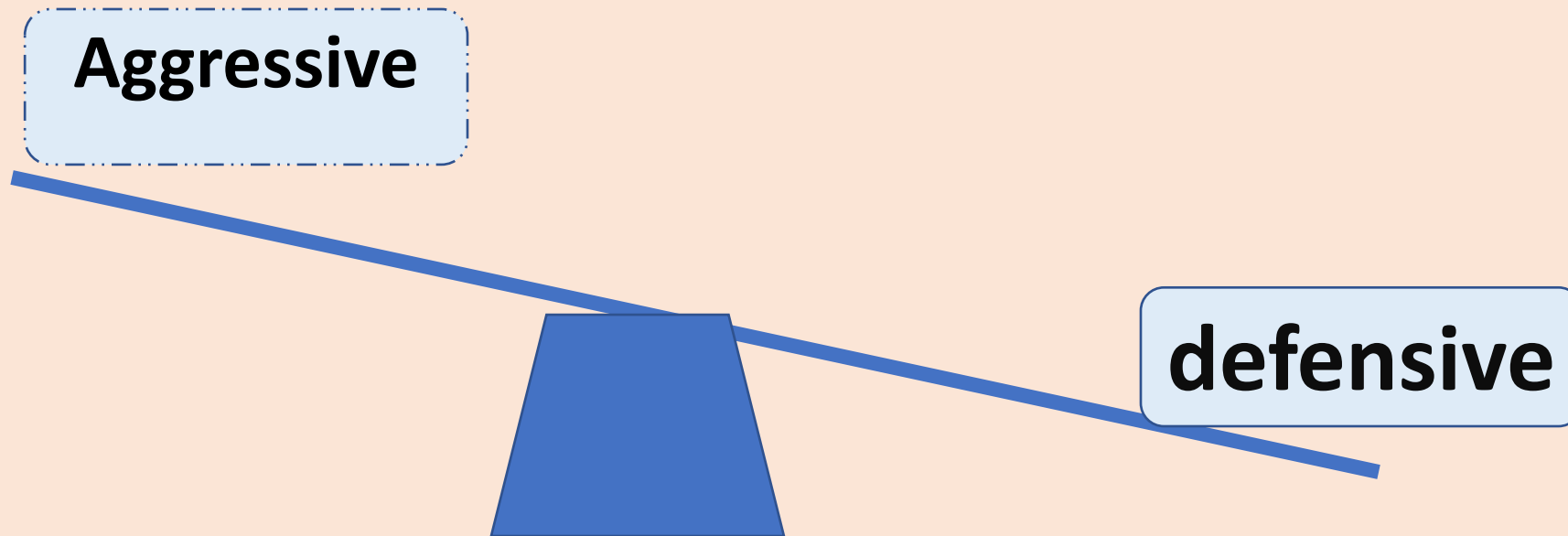
- Drug used for peptic ulcer
- Drug used for constipation, diarrhea
- Drug used for emetic and anti-emetics
- Drugs used as appetizer stimulant, carminatives etc

PEPTIC ULCER:

- Peptic ulcer is abnormal area of mucosa that has been damaged by the pepsin & hydrochloric acid of gastric juice, with consequent inflammation of the underlying and surrounding tissue.
- Erosion may be occur:

It occurs mostly due to imbalance between aggressive and defensive factor:

Aggressive : acid, pepsin, bile, H.pylori



Defensive: gastric mucosa, bicarbonates, PG, Nitric oxide

Different forms of peptic ulcer

- Duodenal ulcer: acid secretion is high
- Gastric ulcer: acid secretion is normal or low but defense is low
- Stress inducing ulcer:
- NSAIDs induced ulcer: inhibition of COX1 in the GIT leads to reduction of PG secretion and cytoprotective effects in gastric mucosa

Stomach secrete about 2.5 ltr of gastric juice (parietal cell)

Gastric acid secretion is regulated by:

Vagus pathway

Gastric acid pathway

Local histamine

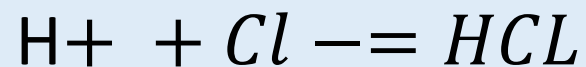
These 3 activate K^+/H^+ ATPase
(proton pump)

caused acid secretion in parietal
cell by

➤ Secretion of H^+ into gastric
lumen

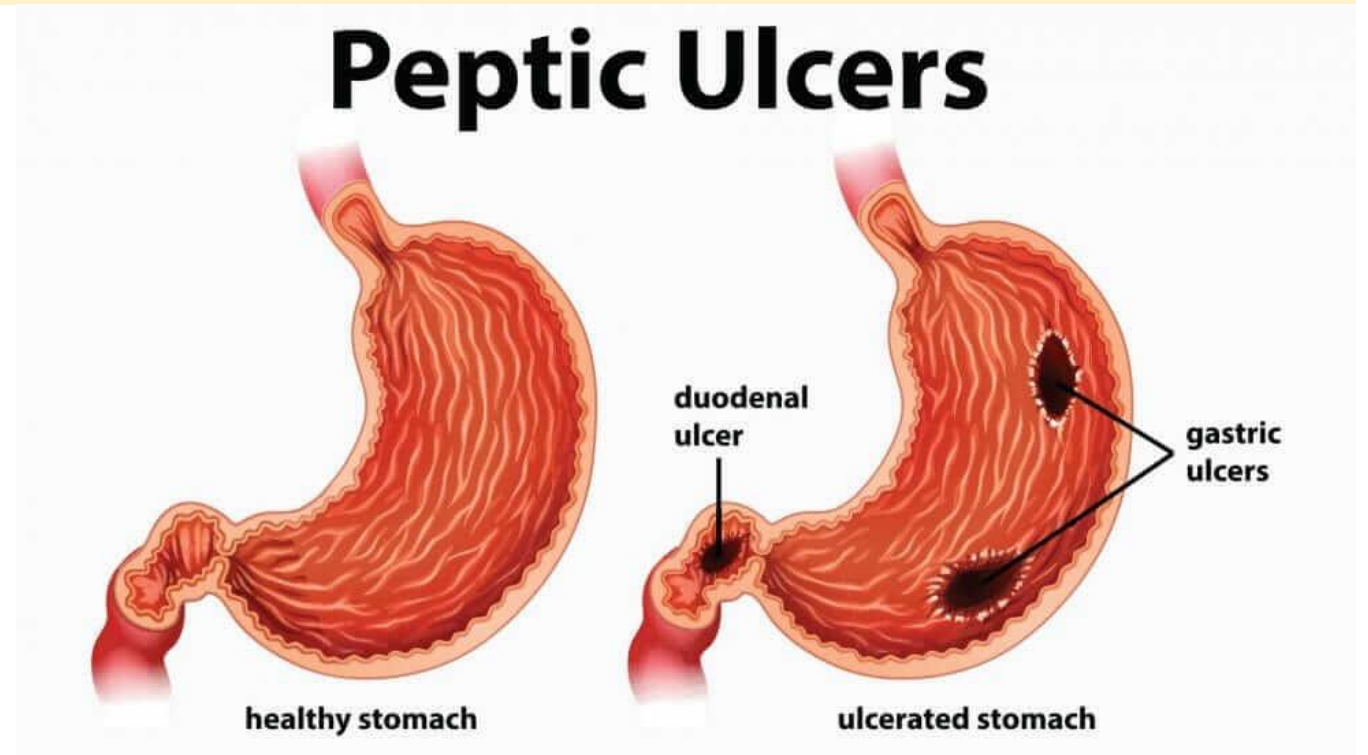
➤ Where as it binds with Cl^-
(derive from plasma)

➤ And form HCL



Symptoms of peptic ulcer:

- Abdominal pain
- Nausea
- Vomiting
- Loss of appetite
- Weight loss
- Bleeding(abnorma;l)



• **CAUSE:**

- H.Pylori infection
- Long term use of Aspirin-NSAIDs
- Stress induced ulcer
- Alcoholism

Risk factors:

- Alcohol(chronic use of alcohol)
- Diet
- Empty stomach

Secretion and regulation of gastric acid

- Mechanism of acid secretion: The H⁺ ion concentration in parietal cell is 3m fold higher than in blood.
- Chloride is secreted against both a concentration & electric gradient.
- Ability of parietal cell to secrete acid is dependent on active transport
- Key player in acid secretion is an H⁺/K⁺ATPase or “Proton pump” located in the canalicular membrane.
- Hydrogen ions are generated within the parietal cell from dissociation of water



Hydroxyl ion formed in this process rapidly combine with CO₂ to form bicarbonate ion, (catalyze by carbonic anhydrase)



- Bicarbonate transported out of the basolateral membrane in exchange for chloride.
- Chloride and pot. ions are transported into the lumen of the cannaliculu by conductance channels
- Hydrogen ion is pumped out of the cell, into the lumen in the exchsng for pot ion through action of proton pump
- Now H⁺ and Cl⁻ together combine to form HCL.

- The parietal cell contains receptor for gastrin, histamine (H2), acetylcholine(M3)

ACh & gastrin together bound to the parietal cell receptor



Cause \uparrow in cytosolic calcium

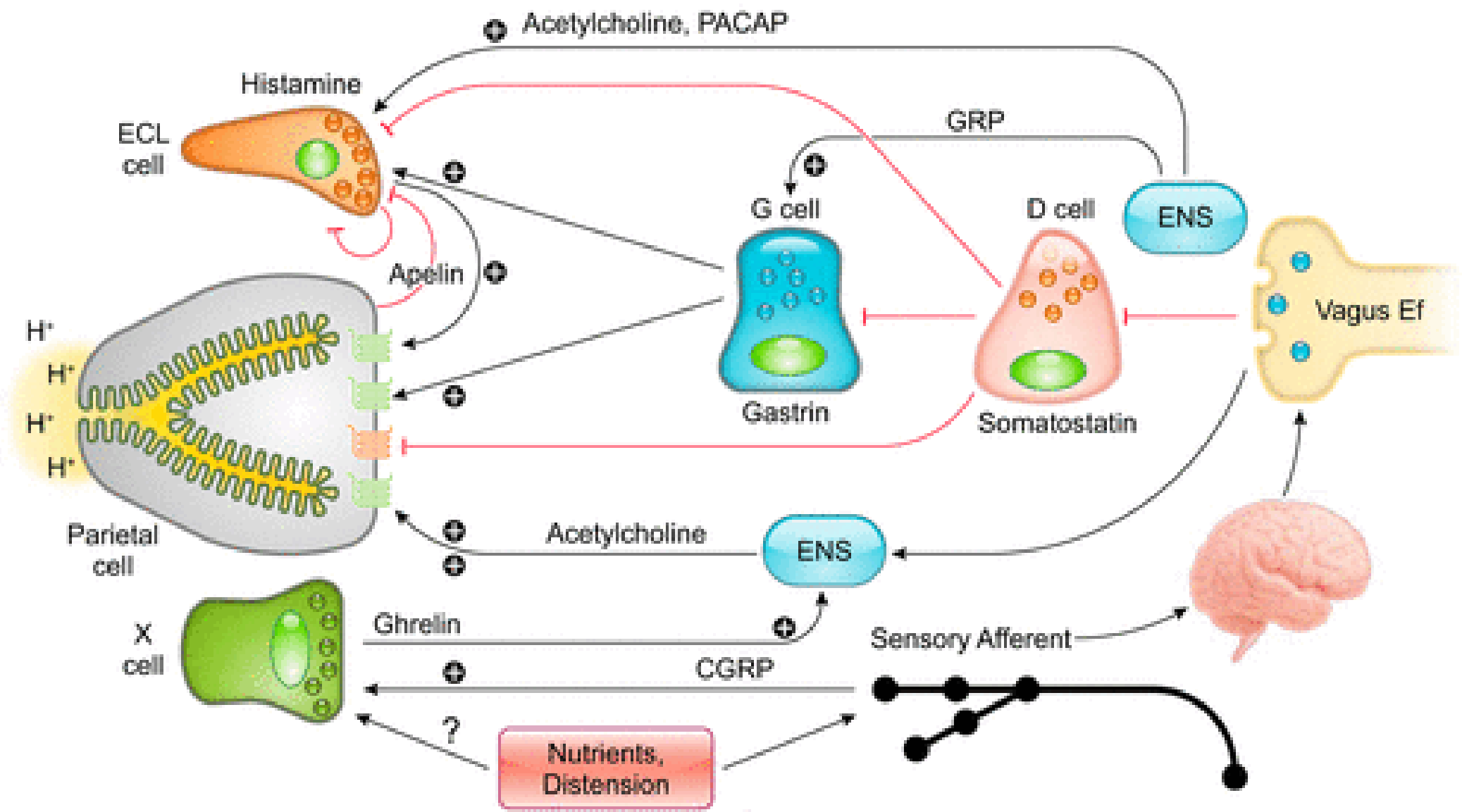


Stimulate protein kinase



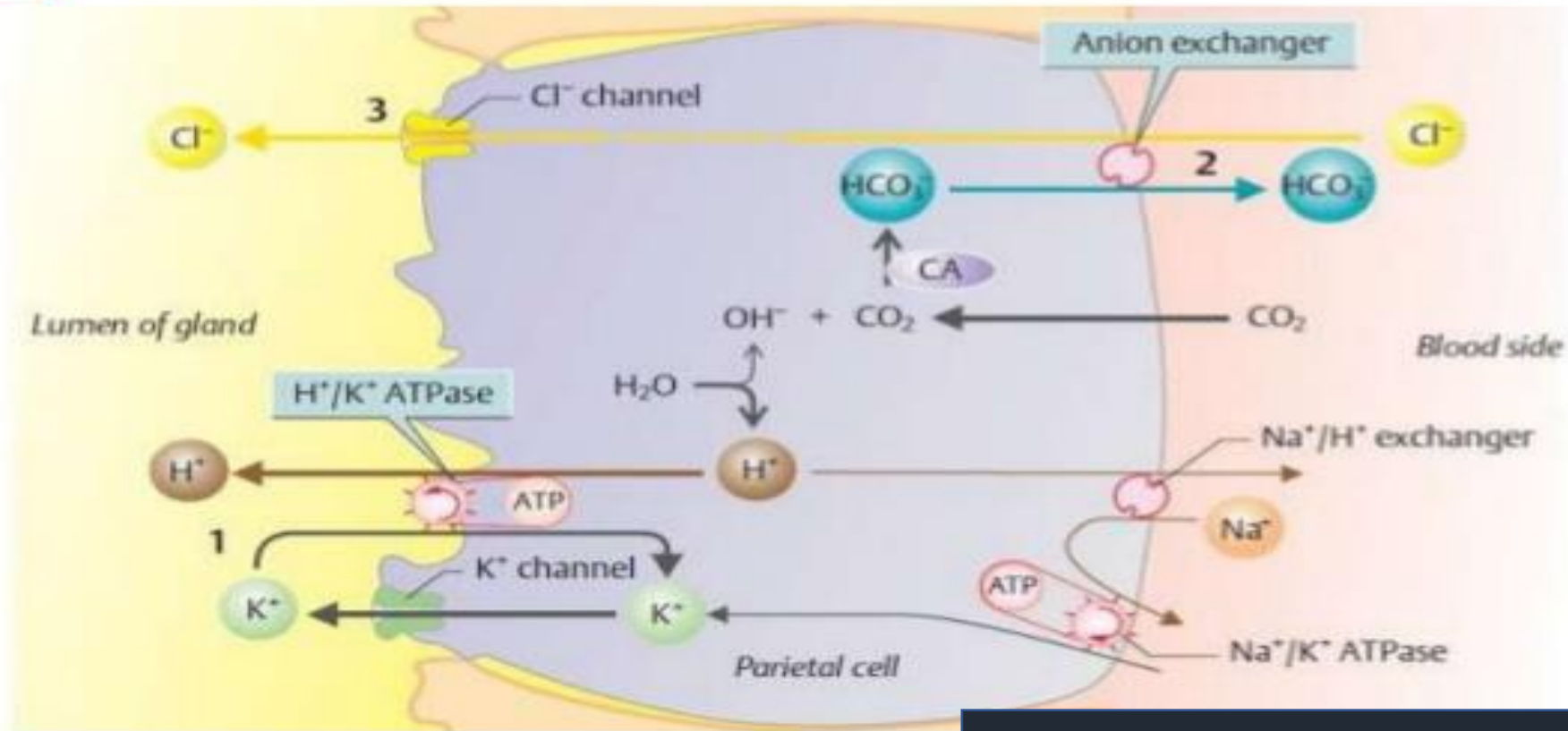
Results stimulation in acid secretion from a H^+/K^+ Atpase (proton pump)
On the canalicular surface

- Parietal cells are gut endocrine cells called as Enterochromaffin like (ECL) CELL.
- ECL have receptor for gastrin and Ach, which stimulate histamine release;
- Histamine binds to the H₂ receptor on the parietal cell resulting in activation of adenylyl cyclase
- This result increase in intracellular cyclic adenosine monophosphate (cAMP) & activates protein kinases:
- Major effect of gastrin upon acid secretion is mediated indirectly through the release of histamine from ECL cells rather than through direct parietal cell stimulation
- Ach provides potent direct parietal cell stimulation





Mechanism Of Acid Secretion



(Gastric acid secretion)

Approaches for the treatment of peptic ulcer are:

Reduction of
gastric acid
secretion

Neutralization
of gastric acid
(Antacids)

Ulcer
protectives:

Anti-H. pylori
drugs:

Reduction of gastric acid secretion:

- (a) **H₂ antihistamines:** Cimetidine, Ranitidine, Famotidine, Roxatidine
- (b) **Proton pump inhibitors:** Omeprazole, Esomeprazole, Lansoprazole, pantoprazole, Rabeprazole, Dexrabeprazole
- (c) **Anticholinergic drugs:** Pirenzepine, Propantheline, Oxyphenonium
- (d) **Prostaglandin analogue:** Misoprostol

H2 RECEPTOR ANTAGONIST:

- Introduced in the year 1970s
- Cimetidine was 1st H2 blocker (prototype)

**COMPETITIVE –
NONCOMPETITIVE**
E
Famotidine

Competitive-
Cimetidine,
Ranitidine, Roxaidine

- H₂ receptor antagonist exhibit competitive inhibition at the parietal cell H₂ receptor
- (in a linear dose dependent manner)
- Highly selective (don't affect H₁ & H₃)
- Vol. of gastric acid secretion & concentration of pepsin also reduced

H₂ antagonist decrease acid secretion stimulated by histamine as well as gastric acid, cholinomimetic agents through two mechanisms;

1. Histamine release from EEC cells by gastrin is blocked from binding to parietal cell H₂ receptor.
2. Direct stimulation of the parietal cell by gastrin or ACh has diminished effect on acid secretion in the presence of H₂ receptor blockade.

Pharmacokinetics :

- Cimetidine, famotidine, ranitidine undergo first pass hepatic metabolism
- Adequately absorbed orally
- Bioavailability 60-80 %
- Cross placenta & breast milk
- 2/3rd is excreted unchanged through urine & biles
- Elimination $t_{1/2}$ is 2-3 hrs

**#DOSE REDUCTION REQUIRED IN
PT WITH MODERATE TO
SEVERE RENAL INSUFFICIENCY**

ADVERSE EFFECTS:

Less than 5%

headache, dizziness, dry mouth,
rashes, bowel upset

Drug interaction:

- Inhibit metabolism of many drugs; theophylline, carbamazepine, phenytoin, phenobarbitone
- Antacid reduced the absorption of all H₂ blockers

CLINICAL USES:

A. Gastroesophageal reflux disease (GERD):

- Pt with infrequent heartburn or dyspepsia may take either antacid or intermittent H2 antagonist
- Antacid provides rapid acid neutralization but effect of antacid is shortb life as compared with H2 antagonist
- H2 antagonist may be taken as prophylactically before meals in an afford to reduce heartburn but PPIs is most preferable

B. Peptic ulcer: PPIs is largely replaced H2 antagonist in the treatment of acute peptic ulcer

- Caused nocturnal acid suppression as ulcer healing.

C. Non-ulcer Dyspepsia:

H2 antagonist are commonly used as OTC drug for treatment of intermittent dyspepsia not caused by peptic ulcers

D. Prevention of bleeding from stress related gastritis

E. Prophylaxis of aspiration pneumonia :

H2 blockers given preoperatively to reduce the risk of aspiration of acidic gastric content during anesthesia and surgeries

MUCOSAL PROTECTIVE AGENTS:

The gastroduodenal mucosa has evolved a number of defense mechanisms to protect itself against the noxious effects of acid and pepsin.

A number of agents that potentiate these mucosal defense mechanisms are available for the prevention and treatment of acid-peptic disorders.

Sucralfate:

Sucralfate is a salt of sucrose complexed to sulfated aluminum hydroxide.

- It is believed that the negatively charged sucrose sulfate binds to positively charged proteins in the base of ulcers or erosion, forming a physical barrier that restricts further caustic damage and stimulates mucosal prostaglandin and bicarbonate secretion.
- Minimally absorbed after oral administration.
- Its action is entirely local.
- Promotes healing of both duodenal and gastric ulcers.
- Healing efficacy has been found similar to cimetidine at 4 weeks, and may be superior in patients who continue to smoke
- **Interactions** Sucralfate adsorbs many drugs and interferes with the absorption of tetracyclines, fluoroquinolones, cimetidine, phenytoin and digoxin.

ANTICHOLINERGIC DRUGS: Pirenzepine, Propantheline, Oxyphenonium

- Anticholinergic drugs show their effect by binding with M3 receptor
- Reduce the volume of gastric juice without raising its pH

Pharmacokinetics:

- Rapidly absorbed from GIT
- Metabolised in liver

Side effects:

- Blurred vision
- Palpitation
- Dry mouth

PROSTAGLANDIN ANALOGUE

- PGE₂ and PGI₂ are produced in the gastric mucosa and appear to serve a protective role by inhibiting acid secretion and promoting mucus
- PGs inhibit gastrin release, increase mucosal blood flow and probably have an ill defined “cytoprotective” action
- They have ability to reinforce the mucus layer covering gastric and duodenal mucosa

- Misoprostol (methylPGE1 ester) is a longer acting synthetic PGE1 derivative
- inhibits acid output dose dependently
- misoprostol is poorer in relieving ulcer pain

Adverse effects:

Prolonged used leads to

- Diarrhoea
- Abdominal cramps
- uterine bleeding
- abortion

USES:

- Use in case of prevention and treatment of NSAID associated gastrointestinal injury

Neutralization of gastric acid (Antacids)

(a) Systemic:

Sodium bicarbonate, Sod. citrate

(b) Nonsystemic:

Magnesium hydroxide, Mag. trisilicate,

Aluminium hydroxide gel,

Magaldrate, Calcium carbonate

- Antacids are weak bases
- React with gastric hydrochloric acid to form a salt and water.
- principal mechanism of action is reduction of intragastric acidity.
- Antacids do not decrease acid production; rather, agents that raise the antral pH to > 4
- The potency of an antacid is generally expressed in terms of its acid neutralizing capacity (ANC),
- which is defined as number of mEq of 1N HCl that are brought to pH 3.5 in 15 min (or 60 min in some tests) by a unit dose of the antacid preparation

SYSTEMIC ANTACID

- Water soluble
- Acts instantly

SODIUM bicarbonate:

- Duration of action is short
- Potent neutralizer (1g– 12mEq HCl)
- pH may rise above 7(may cause systemic alkalosis)
- Absorbed systemically: large dose produces CO₂

- Caused distention, discomfort, belching
- Increase Na⁺ load may worsen edema & CHF

SODIUM CITRATE:

Similar properties with sodium hydroxide

CO₂ is not evolved

NONSYSTEMIC ANTACID:

- Water insoluble
- poorly absorbed,
- basic compounds, reach in stomach to form corresponding chloride salt
- Chloride salt again reacts with intestinal bicarbonates so HCO_3^- is not spared for absorption

MAGNESIUM HYDROXIDE

- Reacts slowly with HCL to form MgCl and water
- No gas is generated
- Belching doesn't occur
- Has low water solubility
- It's a aqueous suspension(**MILK OF MAGNESIA**)
- Unabsorbed magnesium salt may cause an osmotic diarrhea
- (**Soluble Mg salts are used as osmotic purgatives.**)

MAGNESIUM TRISILICATE: Low solubility and reactivity

.

Aluminium hydroxide gel :

- It is a bland, weak and slowly reacting antacid.
- the ANC of a preparation gradually declines on storage
- o, the product from different manufacturers may have differing ANCs; usually it varies from 1–2.5 mEq/g.
- Thus, 5 ml of its suspension may neutralize just 1 mEq HCl
- The Al^{3+} ions relax smooth muscle, thus delays gastric emptying
- causes constipation due to its smooth muscle relaxant
- Alum. hydrox. binds phosphate in the intestine and prevents its absorption—hypophosphatemia occurs on regular use
- **May also cause encephalopathy**
(cause Osteomalacia & Osteoporosis)

Calcium carbonate :

- It is a potent and rapidly acting acid neutralizer ($1 \text{ g} \rightarrow 20 \text{ mEq HCl}$), but ANC of commercial preparations is less and variable due to differing particle size and crystal structure.
- Though it liberates CO_2 in the stomach at a slower rate than NaHCO_3 ,
- It can cause distention and discomfort.
- The Ca^{2+} ions are partly absorbed.

Antacid combinations A combination of two or more antacids is frequently used. These may be superior to any single agent on the following accounts:

- (a) Fast (Mag. hydrox.) and slow (Alum. hydrox.) acting components yield prompt as well as sustained effect.
- (b) Mag. salts are laxative, while alum. salts are constipating: combination may annul each other's action and bowel movement may be least affected.
- (c) Gastric emptying is least affected; while alum. salts tend to delay it, mag./cal. salts tend to hasten it.
- (d) Dose of individual components is reduced; systemic toxicity (dependent on fractional absorption) is minimized.

Drug interactions

- By raising gastric pH and by forming complexes, the non-absorbable antacids decrease the absorption of many drugs:

tetracyclines, iron salts, fluoroquinolones, ketoconazole, H₂ blockers, diazepam, phenothiazines, indomethacin, phenytoin, isoniazid, ethambutol and nitrofurantoin.

- The efficacy of nitrofurantoin is also reduced by alkalinization of urine.

Uses:

Gastroesophageal reflux Antacids afford faster symptom relief than drugs which inhibit acid secretion, but do not provide sustained benefit.

Colloidal bismuth subcitrate (CBS; Tripotassium dicitratobismuthate)

- It is a colloidal bismuth compound; water soluble but precipitates at $\text{pH} < 5$. It is not an antacid but heals 60% ulcers at 4 weeks and 80–90% at 8 weeks.

The mechanism of action of CBS is not clear; probabilities are:

- May increase gastric mucosal PGE₂, mucus and HCO_3^- production.
- May precipitate mucus glycoproteins and coat the ulcer base.
- May detach and inhibit *H.pylori* directly

Most of the ingested CBS passes in the faeces. Small amounts absorbed are excreted in urine. Side effects are diarrhoea, headache and dizziness. Also caused Blackening of tongue & denture

ANTI-HELICOBACTER PYLORI DRUGS

- H. pylori is a gram negative bacillus uniquely adapted to survival in the hostile environment of stomach.
- It has been found that H. pylori is play a vital role in caution of various GI disorder as; dyspepsia, peptic ulcer chronic gastritis
- H. pylori infection starts with a neutrophilic gastritis lasting 7–10 days which is usually asymptomatic.
- Once established, H. pylori generally persists for the life of the host.
- Up to 90% patients of duodenal and gastric ulcer have tested positive for H. pylori.

- Eradication of *H. pylori* concurrently with H2 blocker/PPI therapy of peptic ulcer has been associated with faster ulcer healing and largely prevents ulcer relapse.
- Antimicrobials that are used clinically against *H. pylori* are: amoxicillin, clarithromycin, tetracycline and metronidazole/tinidazole.
- There may be chance of developing resistance to antibiotic (clarithromycin, metronidazole)
- bismuth (CBS) is active against *H. pylori* and resistance does not develop to it, combination regimens including bismuth may be used in case of metronidazole and clarithromycin double resistance
- The PPIs benefit by altering the acid environment for *H. pylori* as well as by direct inhibitory effect.
- One of the PPIs is an integral component of all anti-*H. pylori* regimens along with 2 (triple drug) or 3 (quadruple drug) antimicrobials.

Anti-H. pylori Regimens:

- A number of 3 drug regimens of 1 or 2 weeks are being used.
- One week regimens are adequate for many patients, but 2 week regimens achieve higher (upto 96%) eradication rates.

The US-FDA approved regimen is:

Lansoprazole 30 mg + Amoxicillin 1000 mg + clarithromycin 500 mg, all given twice daily for 2 weeks. This has achieved 86–92% eradication rate.

National Formulary of India (NFI, 2010)

H. pylori eradication regimen of 1 week consisting of:

Omeprazole 40 mg OD + Metronidazole 400 mg TDS + Amoxicillin 500 mg TDS.

- For large ulcers (> 10 mm in diameter) or those complicated by bleeding/perforation the PPI should be continued beyond the 2 weeks-triple drug regimen till complete healing occurs

Quadruple therapy :

CBS 120 mg QID + tetracycline 500 mg QID + metronidazole 400 mg TDS + omeprazole 20 mg BD

“is advocated for eradication failure cases”

- All regimens are complex and expensive, side effects are frequent and compliance is poor.
- Long-term benefits of anti-H. pylori therapy include lowering of ulcer disease prevalence and prevention of gastric carcinoma/lymphoma.

GASTROESOPHAGEAL REFLUX DISEASE (GERD):

- Most common problem is heartburn, sensation of stomach content coming back in the foodpipe;
- Repeated reflux of acid gastric contents into lower 1/3rd of esophagus causes ; esophagitis, erosion, ulcer, pain on swallowing, dysphagia

Stages of GERD:

Stage 1: occasional heartburn

Stage 2: > 3 episodes/week of moderately severe symptoms

Stage 3: Daily/chronic symptoms, disturbed sleep, esophagitis/erosions/stricture/extraesophageal symptoms like laryngitis, hoarseness, dry cough, asthma

Treatment of GERD is depend upon of severity and stage of disorder;

- Stage 3: Daily/chronic symptoms, disturbed sleep, esophagitis/erosions/stricture/extraesophageal symptoms like laryngitis, hoarseness, dry cough, asthma
- H2 blockers They reduce acidity of gastric contents and have no effect on LES tone.
- Antacids Their use in GERD is limited to occasional or intercurrent relief of heartburn
- Prokinetic drugs Metoclopramide, cisapride and other prokinetic drugs may relieve regurgitation and heartburn by increasing LES tone, improving esophageal clearance and facilitating gastric emptying

➤ **Sodium alginate:(most prominently used)**

- It forms a thick frothy layer which floats on the gastric contents like a raft may prevent contact of acid with esophageal mucosa.
- It has no effect on LES tone.**(Lower esophageal sphincter)**
- Combination of alginate with antacids may be used in place of antacids alone, but real benefit is marginal.