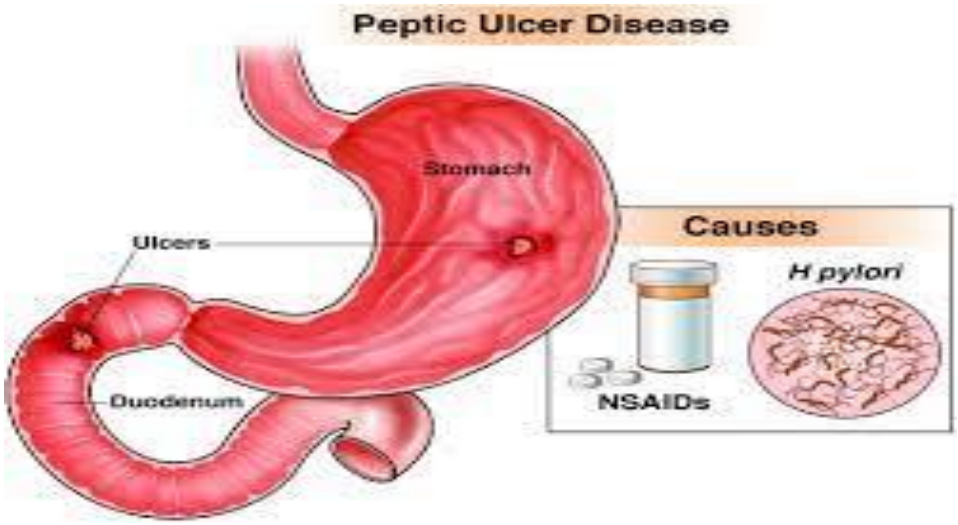
Gastrointestinal Pharmacology



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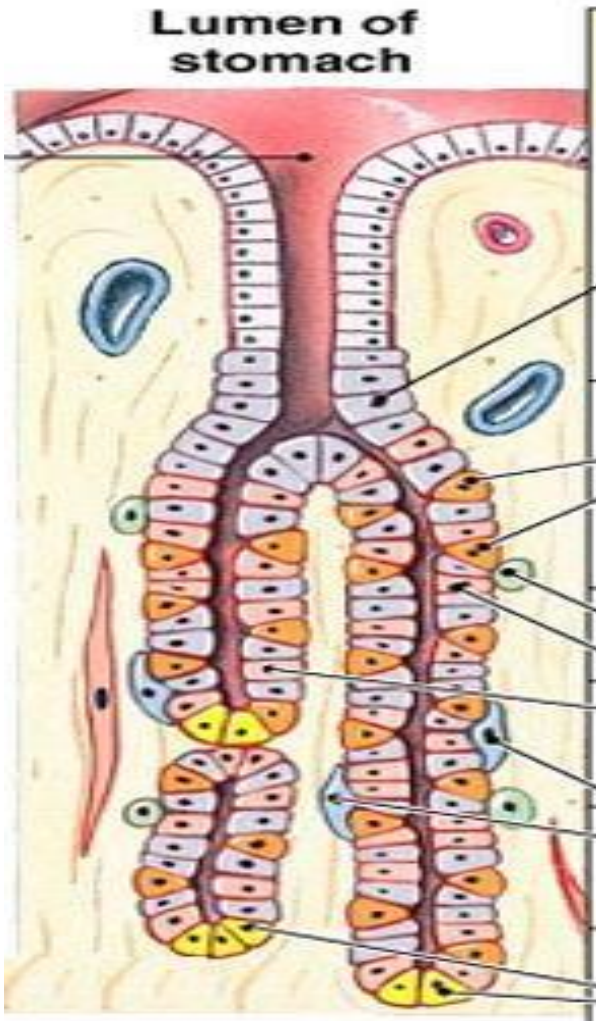


Cell Types	*Substance Secreted*
Mucous neck cell	Mucus (protects lining)
	Bicarbonate
Parietal cells	Gastric acid (HCl)
	Intrinsic factor (Ca++ absorption)
Enterochromaffin-like cell	Histamine (stimulates acid)
Chief cells	Pepsin(ogen)
	Gastric lipase
D cells	Somatostatin (inhibits acid)
G cells	Gastrin (stimulates acid)

GASTRIC GLANDS

PEPTIC ULCER

Definition: ulceration of the duodenum or stomach due to imbalance between local invasive force (e.g. HCl and pepsin) and protective mechanisms.

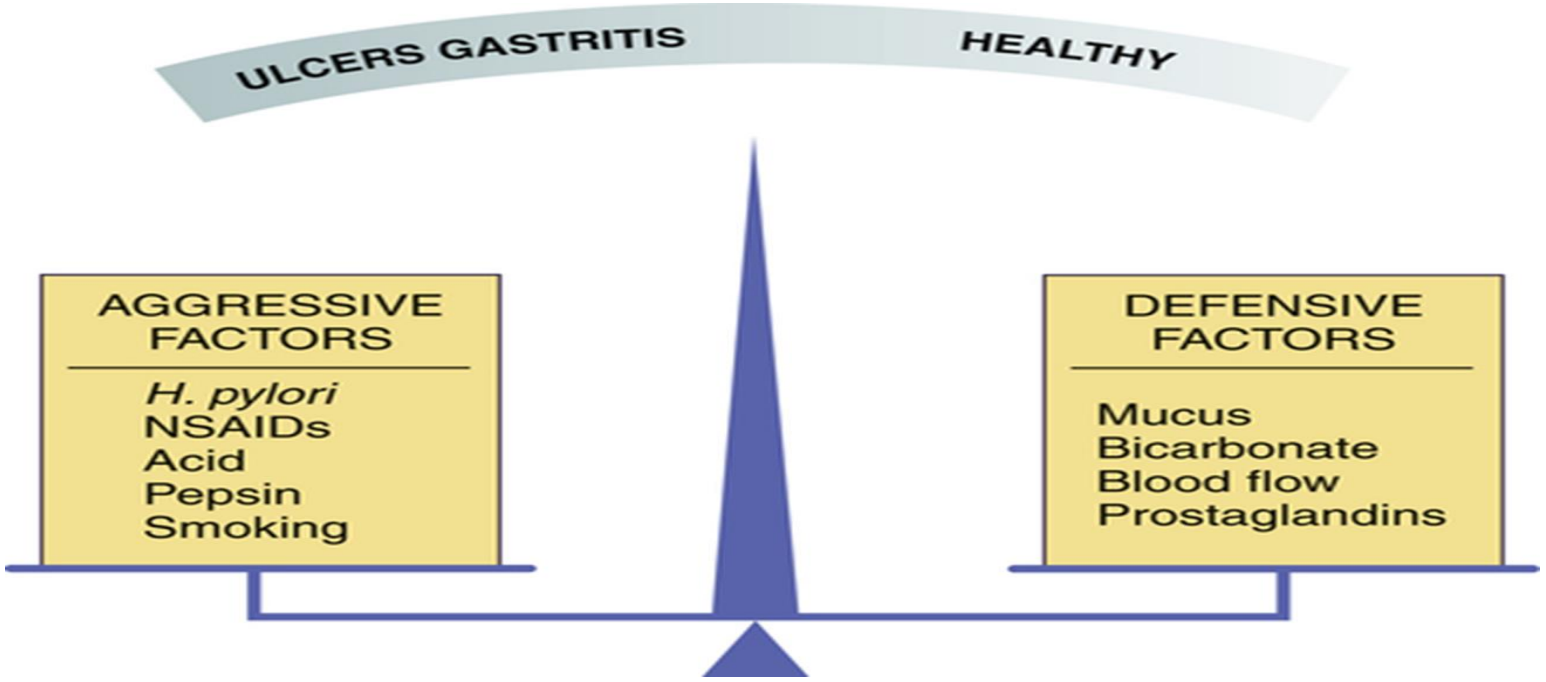
Invasive factors:

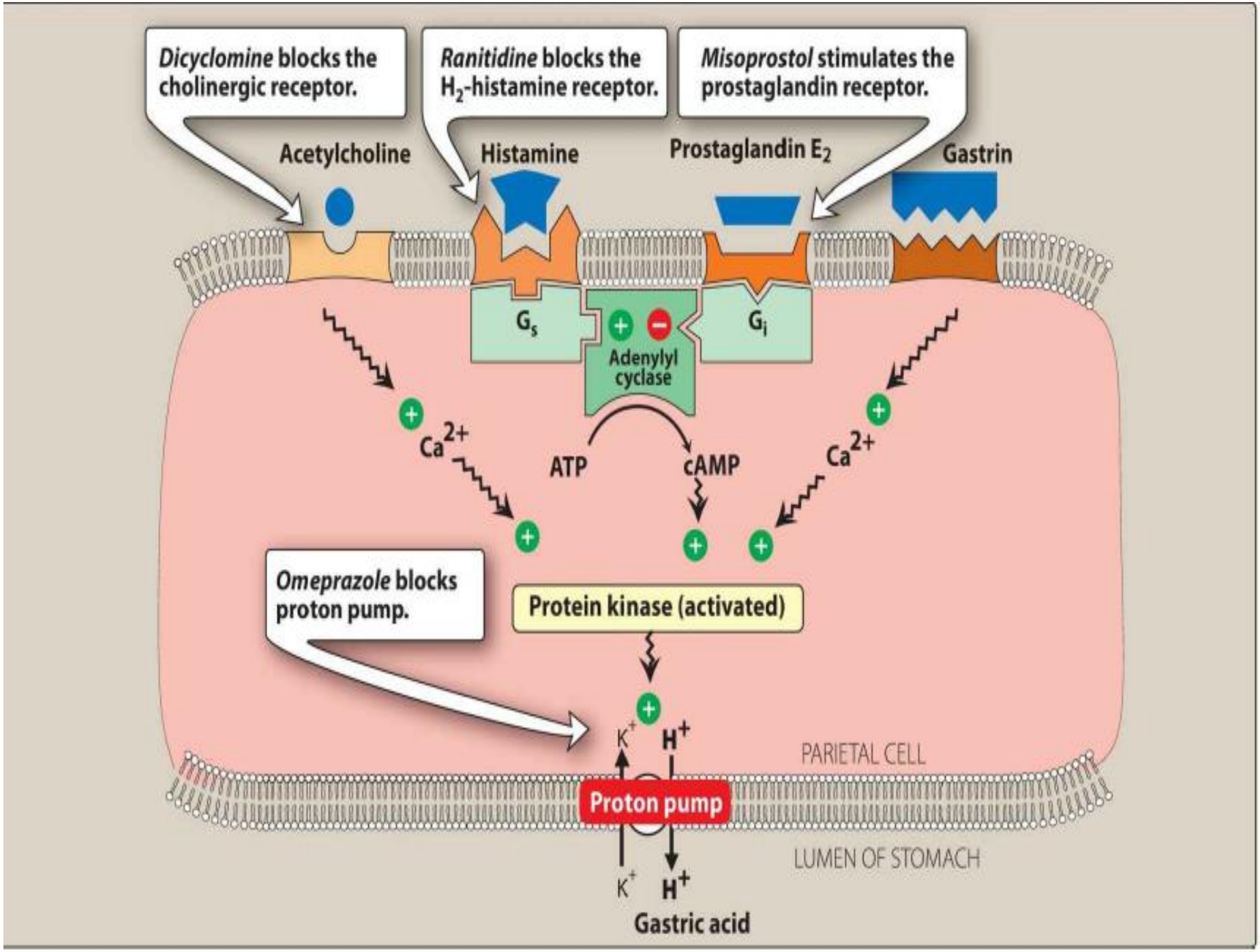
- Stress: ↑ HCl and pepsin secretion by parietal cells.
- Diet: coffee, alcohol and spices.
- **Drugs:** NSAIDs, corticosteroids, morphine, methylxanthines, etc.
- **Infection** with ***Helicobacter pylori.***

  H. pylori is spiral gram –ve flagellates found in the antrum of human stomach. Certain enzymes and toxins produced by the bacteria cause tissue damage. Infection with *H. pylori* can be diagnosed by endoscopic biopsy or serological markers.

Defensive mechanisms:

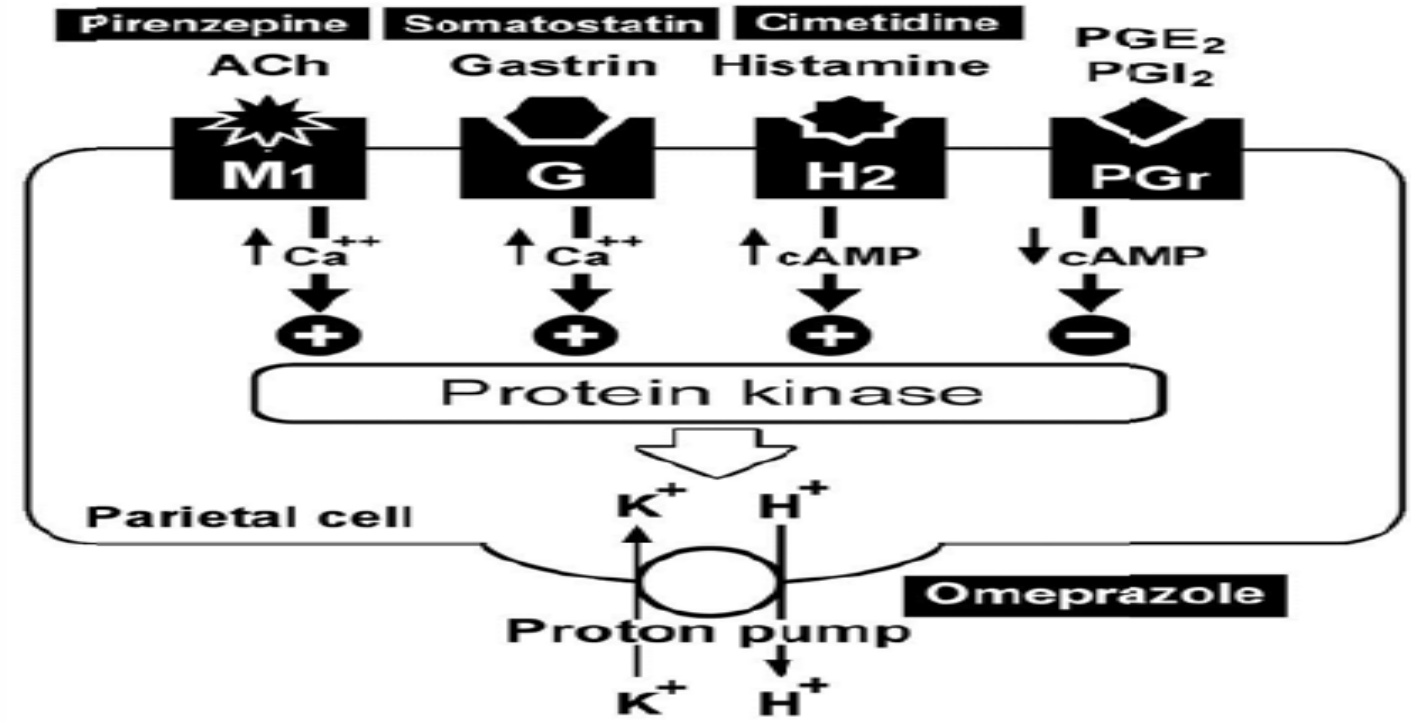
- Mucus production by gastric mucosa.
- Pancreatic bicarbonate secretion.
- Good mucosal blood flow.
- Local PGE_2 and PGI_2 production.

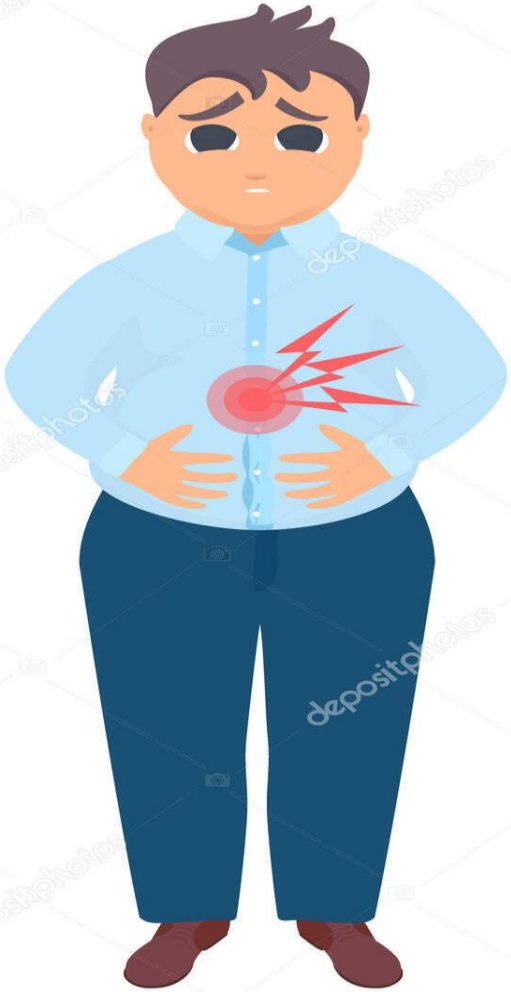



Dicyclomine blocks the cholinergic receptor.
Ranitidine blocks the H_2-histamine receptor.
Misoprostol stimulates the prostaglandin receptor.
Acetylcholine
Histamine
Prostaglandin E_2
Gastrin
G_s
G_i
Adenylyl cyclase
Ca^{2+}
ATP
cAMP
Ca^{2+}
Omeprazole blocks proton pump.
Protein kinase (activated)
K^+
H^+
PARIETAL CELL
Proton pump
LUMEN OF STOMACH
K^+
H^+
Gastric acid

Both Ca^{2+} and cAMP activate H^+/K^+ *ATPase* at the membrane of the parietal cell to secrete H^+ into the gastric lumen **"proton pump"**.

- **PGE_2** and **PGI_2:** act on PG receptors → ↓ cAMP → ↓ HCl secretion.





PEPTIC ULCER

CAUSES

- NSAIDs (non-steroidal anti-inflammatory drugs)
- Helicobacter pylori

SYMPTOMS

- Upper abdominal pain
- Nausea
- Bloating
- Lack of appetite
- Weight loss
- Heartburn

Drugs Used to Treat Peptic Ulcer Disease(PUD)

- The two main causes of peptic ulcer disease are infection with gram-negative Helicobacter pylori and the use of nonsteroidal anti-inflammatory drugs (NSAIDs). Increased hydrochloric acid (HCl) secretion and inadequate mucosal defense against gastric acid also play a role.

Treatment approaches include 1) eradicating the H. pylori infection, 2) reducing secretion of gastric acid with the use of PPIs or H2 receptor antagonists, and/or 3) providing agents that protect the gastric mucosa from damage, such as *misoprostol* and *sucralfate*

Therapy of peptic ulcer

Non-drug therapy = life style modification

- Rest and **S**edation: they improve healing and relief pain of DU.
- Stop **S**moking, **S**pices, alcohol, coffee, and tea: because they ↑ HCl.
- Avoid **S**tress: because stress ↑ HCl.
- Avoid ulcerogenic drugs: e.g. NSAIDs.
- Diet:
  - Frequent small meals in DU in order to buffer high acidity.
  - Encourage milk and fats.
  - Avoid **S**pices and fried food

Pharmacological therapy

- **Drugs that neutralize HCl:** antacids
- **Drugs that ↓ HCl secretion:**
  - Selective M_1 blockers: pirenzepine, telenzepine.
  - H_2 blockers: cimetidine, ranitidine, famotidine.
  - Proton pump inhibitors: omeprazole, lanzoprazole, etc.

- **Drugs that ↑ mucosal defense mechanisms:**
  - Sucralfate
  - Colloid bismuth compounds: e.g. bismuth subcitrate.
  - Carbenoxolone
  - PGE_1 analogues: misoprostol.

ANTACIDS

- Antacids are weak bases that are taken orally and partially neutralize gastric acid and reduce pepsin activity.
- They are used as **symptomatic relief** of hyperacidity and should **not** be used as long-term treatment.

Sodium bicarbonate	Calcium carbonate	Magnesium and aluminum salts (Mg hydroxide and Aluminium hydroxide)
▪ It can be **absorbed** systemically leading to salt & water retention, and metabolic alkalosis. ▪ It is contraindicated in hypertension and heart failure. ▪ It has **rapid** onset and short duration.	▪ **Partially** absorbed ant-acid. ▪ Ca^{2+} may act directly to stimulate gastrin secre-tion leading to acid rebound. ▪ It is contraindicated in hypercalcemia and renal stones.	▪ They are **poorly** ab-sorbed from GIT and have no systemic effects. ▪ The unabsorbed Mg salts cause osmotic **di-arrhea**; the unabsorbed Al salts cause **constipation**. ▪ They have **slow** onset.

Adverse effects

- **Change in bowel habits:** Al^{3+} hydroxide causes *constipation*, while Mg^{2+} hydroxide cause *diarrhea*. For this reason, both salts are combined together to manage this problem.

- **Decrease absorption of other drugs:** the metal ion in some preparations can chelate other drugs especially tetracycline, digitalis and iron.

H2 receptor antagonists:

By competitively blocking the binding of histamine to H2 receptors, these agents reduce the secretion of gastric acid. The four drugs —*cimetidine* , *famotidine* , *nizatidine* and *ranitidine* —inhibit basal, food-stimulated, and nocturnal secretion of gastric acid, reducing acid secretion by approximately 70%. *Cimetidine* was the first H2 receptor antagonist. However, its utility is limited by its adverse effect profile and drug–drug interactions.

Therapeutic uses

1. **Peptic ulcers**

2-Acute stress ulcers: These drugs are given as an intravenous infusion to prevent and manage acute stress ulcers associated with high-risk patients in the intensive care setting.

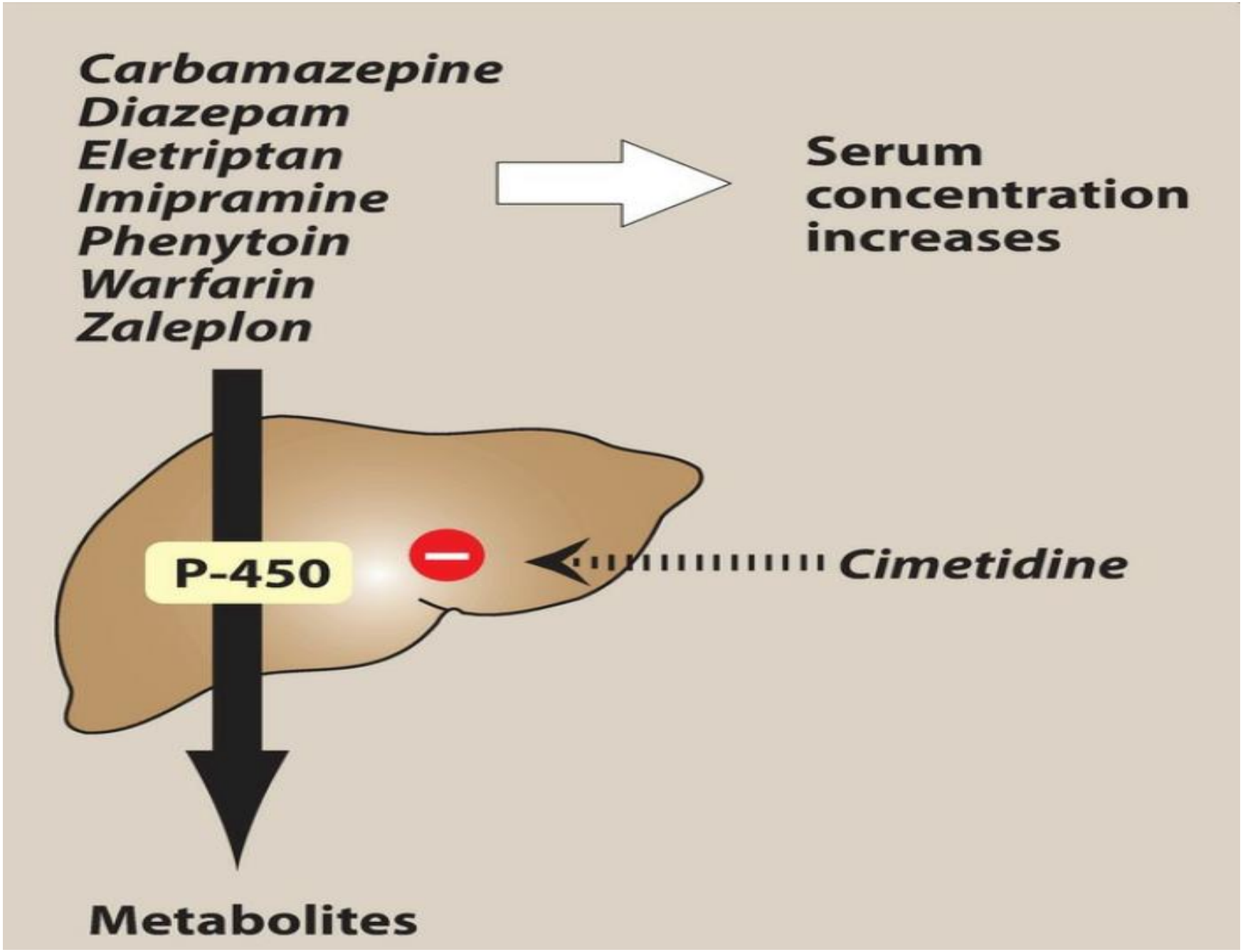
3- Gastroesophageal reflux disease(GERD)or heartburn

Adverse effects

- In general, the H2 receptor antagonists are well tolerated. However, ***cimetidine*** can have endocrine effects, such as gynecomastia and galactorrhea (continuous release/discharge of milk), because it acts as antiandrogen.
- central nervous system effects such as confusion and altered mentation occur primarily in elderly patients and after intravenous administration

- H2 receptor antagonists may reduce the efficacy of drugs that require an acidic environment for absorption, such as *ketoconazole.*
- *Cimetidine* inhibits several cytochrome P450

isoenzymes and can interfere with the metabolism of many drugs, such as *warfarin*, *phenytoin*, and *clopidogrel*


Carbamazepine
Diazepam
Eletriptan
Imipramine
Phenytoin
Warfarin
Zaleplon
Serum concentration increases
P-450
Cimetidine
Metabolites

Inhibitors of the H+/K+-ATPase proton pump

The PPIs bind to the H+/K+-ATPase enzyme system (proton pump) and suppress the secretion of hydrogen ions into the gastric lumen. The membrane-bound proton pump is the final step in the secretion of gastric acid . The available PPIs include *dexlansoprazole , esomeprazole, lansoprazole , omeprazole, pantoprazole* and *rabeprazole*


Nexium
40mg
esomeprazole
14 tablets
Nexium 20 mg


Delayed-release Capsules
DEXILANT® 60mg
Delayed-release
Capsules
Dexlansoprazole
Oral use
28 capsules


Omeprazole Capsules 20 mg
APRAZOLE - 20
Omeprazole Capsules 40 mg
APRAZOLE - 40


Pariet® 20 mg
Enteric Tablet
28 enterik tablet
janssen


Pantoprazole
20mg Gastro-resistant Tablets
Pantoprazole
Oral use
20 mg

Actions:

These agents are prodrugs with an **acid-resistant enteric coating to protect them from premature degradation by gastric acid**. The coating is removed in the alkaline duodenum, and the prodrug, a weak base, is absorbed and transported to the parietal cell. There, it is converted to the active drug and forms a stable covalent bond with the H+/K+-ATPase enzyme. It takes about 18 hours for the enzyme to be resynthesized, and acid secretion is inhibited during this time. At standard doses, PPIs inhibit both basal and stimulated gastric acid secretion by more than 90%.An **oral product containing *omeprazole* combined with *sodium bicarbonate* for faster absorption is also available**.

Therapeutic uses:

The PPIs are **superior to the H2 antagonists** in suppressing acid production and healing ulcers.

1-treatment of GERD, erosive esophagitis, active peptic ulcer,

2-Zollinger-Ellison syndrome.(gastrin-secreting tumor of the pancreas which ↑ HCl secretion): usually larger doses are required.)

3-PPIs reduce the risk of bleeding from ulcers caused by *aspirin* and other NSAIDs and may be used for prevention or treatment of NSAID-induced ulcers.

4-PPIs are also used for stress ulcer prophylaxis and management.

5-Finally, PPIs are combined with antimicrobial regimens used to eradicate H. pylori.

- **Pharmacokinetics**
- These agents are effective orally. For maximum effect, PPIs should be taken 30 to 60 minutes before breakfast or the largest meal of the day. [*Dexlansoprazole* has a dual delayed-release formulation and can be taken without regard to food.] *Esomeprazole*, *lansoprazole*, and *pantoprazole* are available in intravenous formulations. Although the plasma half-life of these agents is only a few hours, they have a long duration of action due to covalent bonding with the H+/K+-ATPase enzyme. Metabolites of these agents are excreted in urine and feces.

Adverse effects

The PPIs are generally well tolerated.

1- *Omeprazole* and *esomeprazole* may decrease the effectiveness of *clopidogrel* because they inhibit CYP2C19 and prevent the conversion of *clopidogrel* to its active metabolite.Concomitant use of these PPIs with *clopidogrel* is not recommended.

2- PPIs may increase the risk of fractures (osteoporosis), particularly if the duration of use is 1 year or greater

3- Prolonged acid suppression with PPIs (and H2 receptor antagonists) may result in low vitamin B12 because acid is required for its absorption in a complex with intrinsic factor.

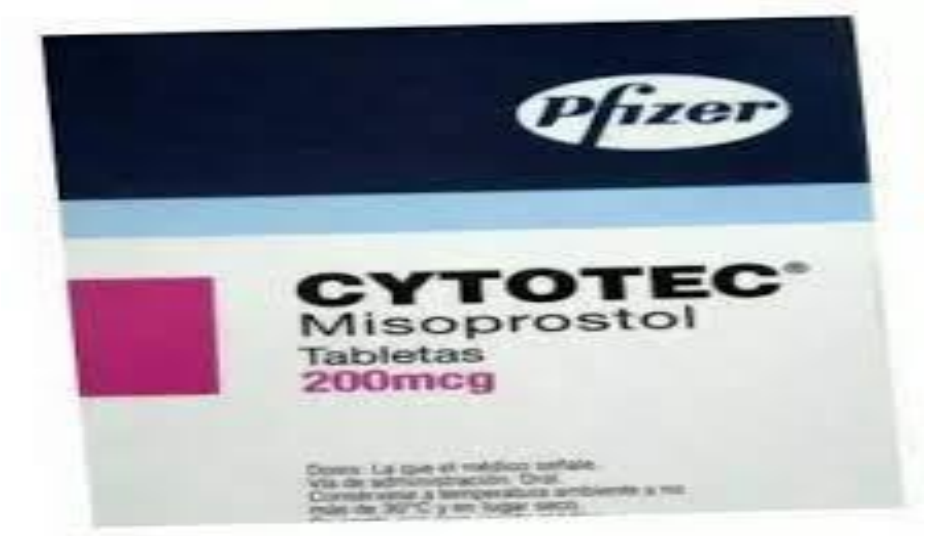
4- Diarrhea and Clostridium difficile colitis may occur in patients receiving PPIs.

5-Additional adverse effects may include hypomagnesemia and an increased incidence of pneumonia.

Prostaglandins

Prostaglandin E, produced by the gastric mucosa, inhibits secretion of acid and stimulates secretion of mucus and bicarbonate (cytoprotective effect). A deficiency of prostaglandins is thought to be involved in the pathogenesis of peptic ulcers. ***Misoprostol*** an analog of prostaglandin E1, is approved for the prevention of NSAID-induced gastric ulcers

Misoprostol is contraindicated in pregnancy, since it can stimulate uterine contractions and cause miscarriage. Dose-related **diarrhea** is the most common adverse effect and limits the use of this agent. Thus, PPIs are preferred agents for the prevention of NSAID-induced ulcers.



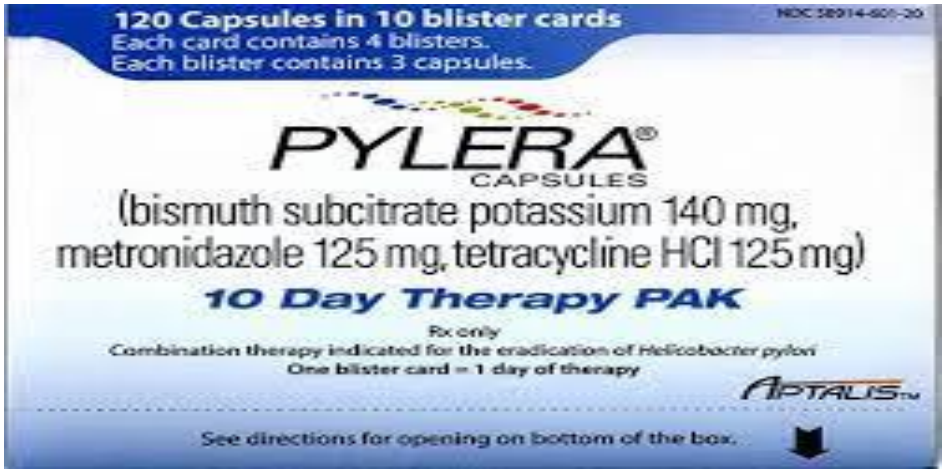
Mucosal protective agents

1. Sucralfate

This complex of *aluminum hydroxide* and sulfated sucrose binds to positively charged groups in proteins of both normal and necrotic mucosa. By forming complex gels with epithelial cells, *sucralfate* creates a physical barrier that protects the ulcer from pepsin and acid, allowing the ulcer to heal. Although *sucralfate* is effective for the treatment of duodenal ulcers and prevention of stress ulcers, its use is limited due to the need for multiple daily dosing, drug–drug interactions, and availability of more effective agents. Because it requires an acidic pH for activation, *sucralfate* should not be administered with PPIs, H2 antagonists, or antacids. *Sucralfate* is well tolerated, but it can bind to other drugs and interfere with their absorption.

2. Bismuth subsalicylate

This agent is used as a component of quadruple therapy to heal H. pylori-related peptic ulcers. In addition to its antimicrobial actions, it inhibits the activity of pepsin, increases secretion of mucus, and interacts with glycoprotein in necrotic mucosal tissue to coat and protect the ulcer.



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