Drugs Used in the Treatment of Gastrointestinal Diseases.

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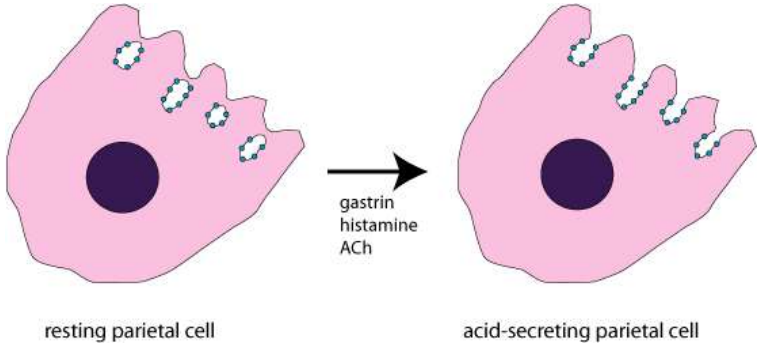
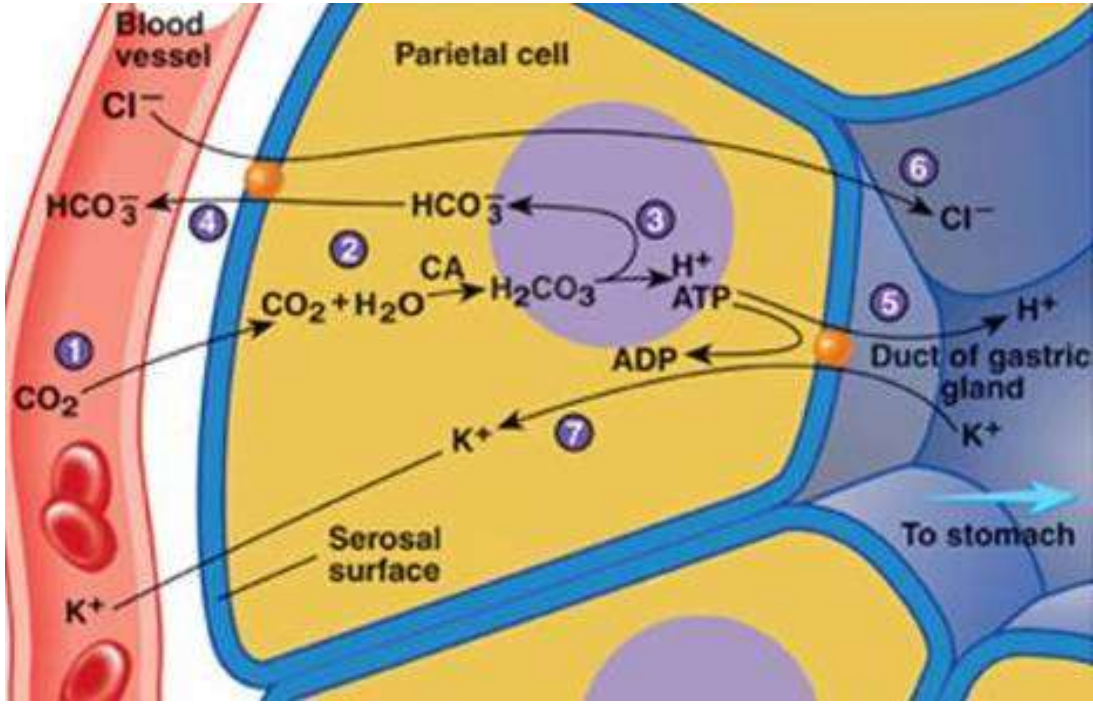
Physiology of gastric Secretion



Parietal cells secrete **2** liters of acid/ day.
Optimal pH (between **1.8-3.5**) for the function of the digestive enzyme pepsin.

Stimulation of acid secretion involves **translocation** of **H+/K+-ATPase** to the apical membrane of **parietal cell.**

H+/K+-ATPase (**proton pump**) uses the energy derived from ATP hydrolysis to pump H+ into the lumen in exchange for potassium ions.
Chloride and hydrogen ions are secreted separately from the cytoplasm of parietal cells and mixed in the canaliculi.

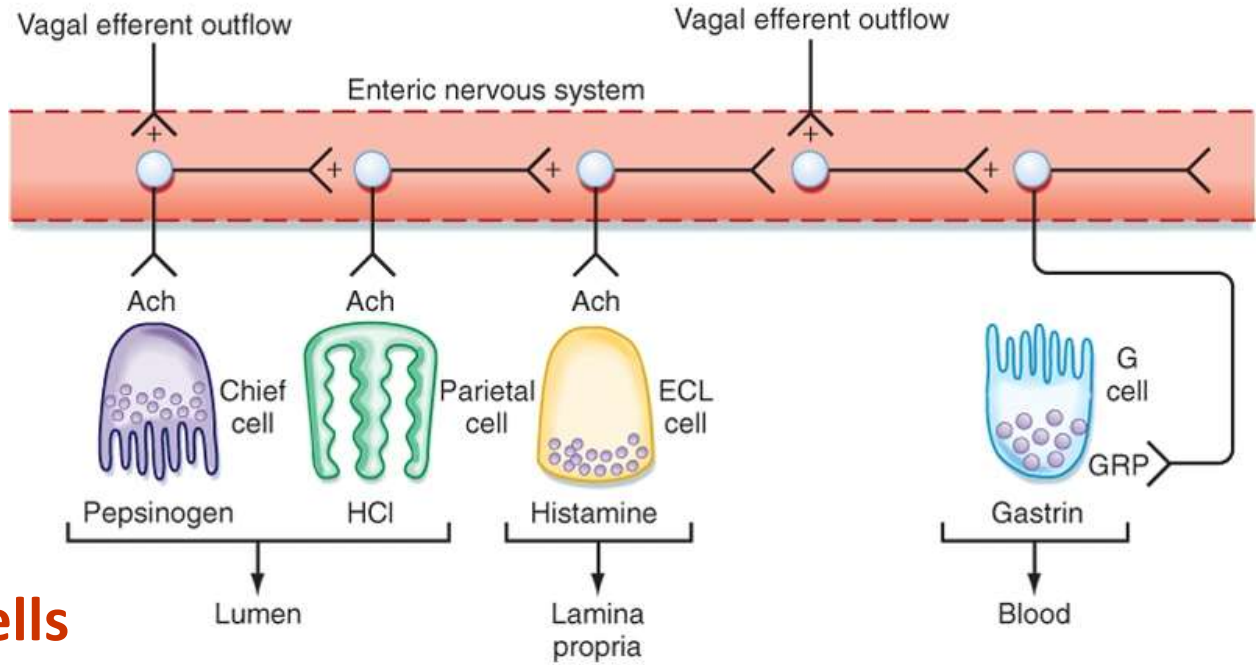


Stimulants of acid secretion:

1-**Ach** from **enteric neurons**.

2-Histamine from **ECL** (**enterochromaffin - like**) **cells**.

3-Gastrin released by **G cells.**



Gastrin releasing peptide (**GRP**)

Somatostatin in **D cells inhibits acid secretion.**

Gastric pH < 3 --> gastric D cells release somatostatin

It inhibits acid secretion by:

1-direct effects on parietal cells.

2- inhibiting release of histamine & gastrin.

Three phases in gastric acid secretion.

Cephalic Phase:

sight, smell, taste or thought of food,

activate enteric neurons via vagus. In humans, the major effect of **gastrin** is indirect through the release of histamine from ECL cells not through direct parietal cell stimulation.

Gastric Phase:

Food stretch stomach walls

activating a neural reflex

to stimulate acid secretion.

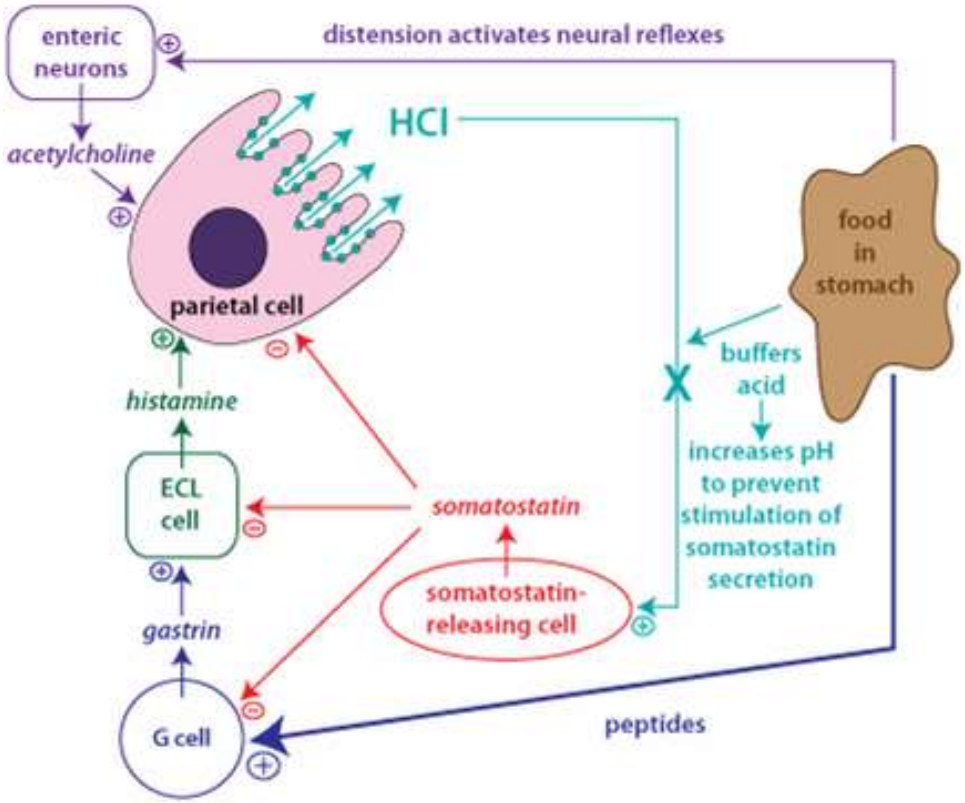
Peptides & amino acids stimulate

G cells to release gastrin.

Food acts as a buffer, raising the

pH & thus removing the stimulus

for somatostatin secretion .

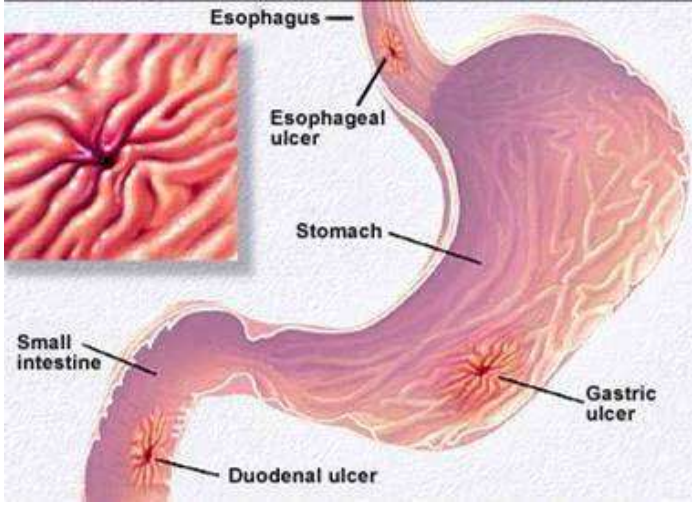


Intestinal Phase:

Once chyme enters the duodenum, it activates negative feedback mechanisms to reduce acid secretion.

Peptic ulcer

A defect in the lining of
the stomach or the duodenum.



Causes of Peptic Ulcer:

Helicobacter pylori (most common).

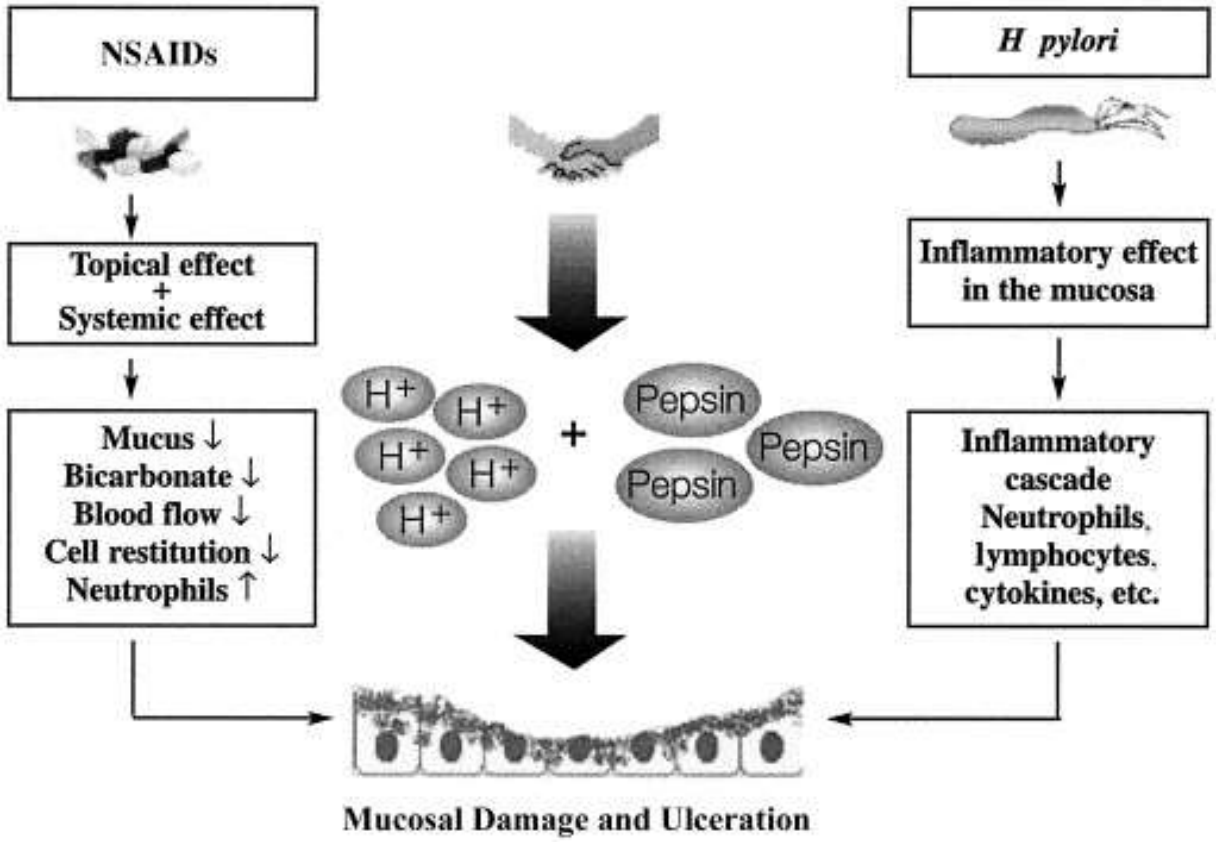
Drugs such as aspirin
& other NSAIDs

Other factors:

Smoking,
Stress,
alcohol.
Gastrinomas

Zollinger Ellison syndrome

a rare gastrin-secreting tumors.



Symptoms:

burning pain in stomach between meals or at night, bloating, heartburn, nausea or vomiting.

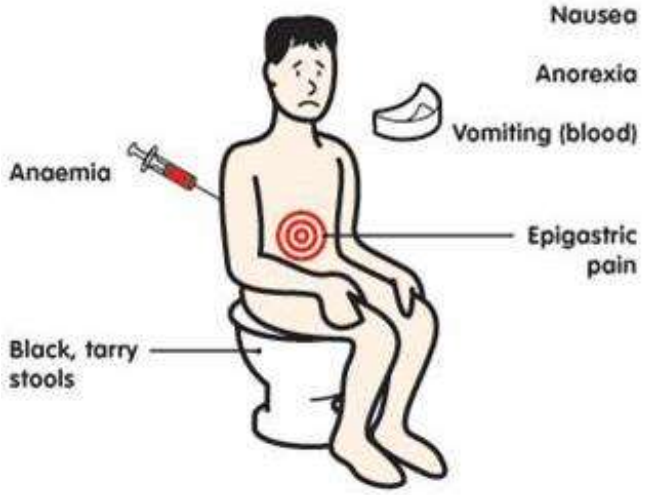
In severe cases, symptoms include:

Dark or black stool (due to bleeding)

Vomiting blood

Weight loss & severe pain

in the mid to upper abdomen.



Complications of peptic ulcer

Gastrointestinal bleeding.

(Sudden large bleeding can be life threatening).

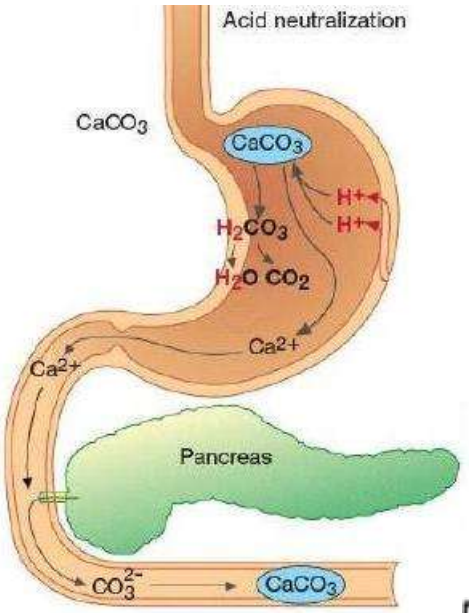
Cancer (Helicobacter pylori as the etiological factor)

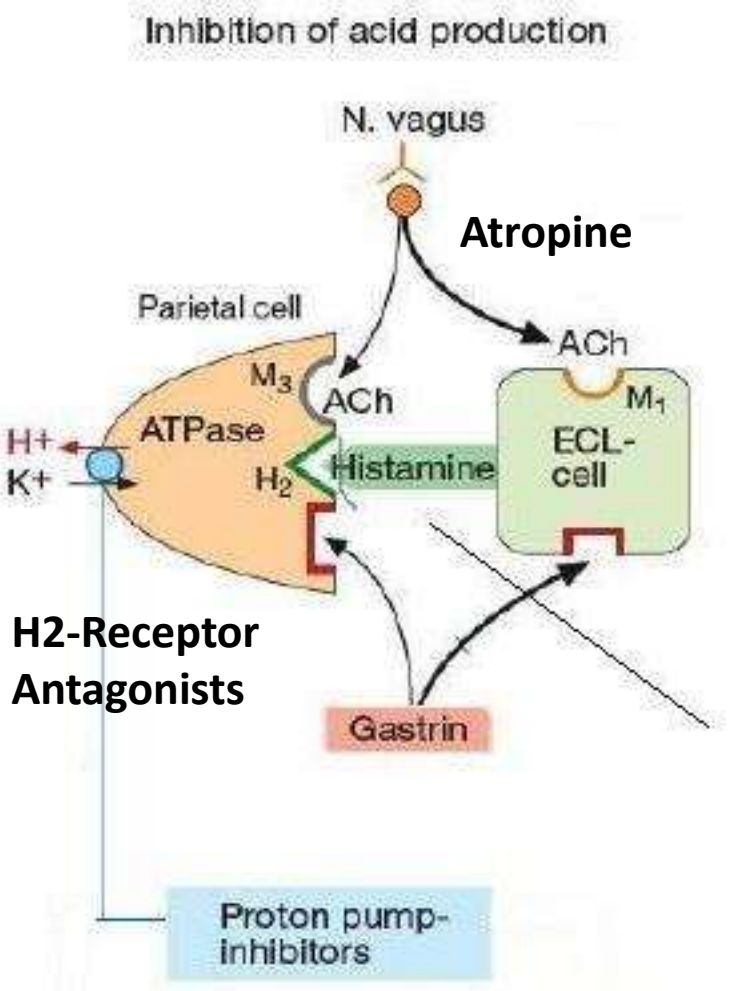
Perforation (hole in the wall) Penetration.

Treatment options

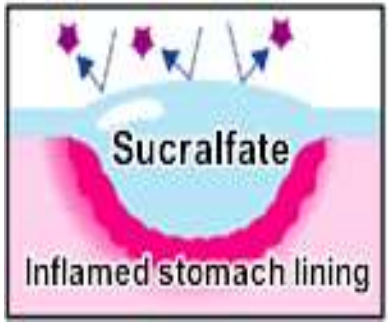
Reduce acid secretion or

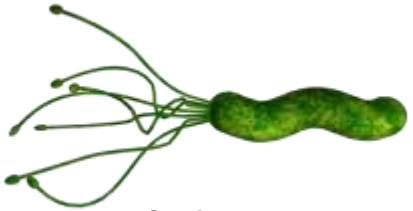
Neutralize acid in the lumen





Protect the mucosa from acid destruction





Antibiotics to eradicate *Helicobacter pylori.* If this is successful then the ulcer should begin to heal on its own.

Neutralization of acid (Antacids)

Nonprescription remedies for treatment of heartburn & dyspepsia.

Given 1 hour after a meal effectively neutralizes gastric acid for up to 2 hours.

$$AL(OH)3 + HCl \text{ -----> } ALCl3 + H2O$$

$$2HCl + Mg(OH)2 \text{ ----> } MgCl2 + 2H2O$$

Aluminum antacids cause constipation, interfere with absorption of many drugs.

Magnesium antacids have laxative action; diarrhea.

ionic magnesium stimulates gastric release (acid rebound)

Magnesium trisilicate slow-acting antacid

Combination of Magnesium & aluminum antacids are most commonly used (No diarrhea or constipation).

Calcium carbonate

associated with "acid rebound"

with excessive chronic use, it may cause milk-alkali syndrome with elevation of serum calcium, phosphate , urea, nitrogen, creatinin & bicarbonate levels.

$2HCl + CaCO_3 \rightarrow CaCl_2 + \mathbf{CO_2} + H_2O$

Sodium bicarbonate

-Should be avoided as it aggravate CHF & counteracts diuretic therapy for hypertension,

-Short duration of action, followed by acid rebound.

-Highly absorbed, potentially causing metabolic alkalosis.

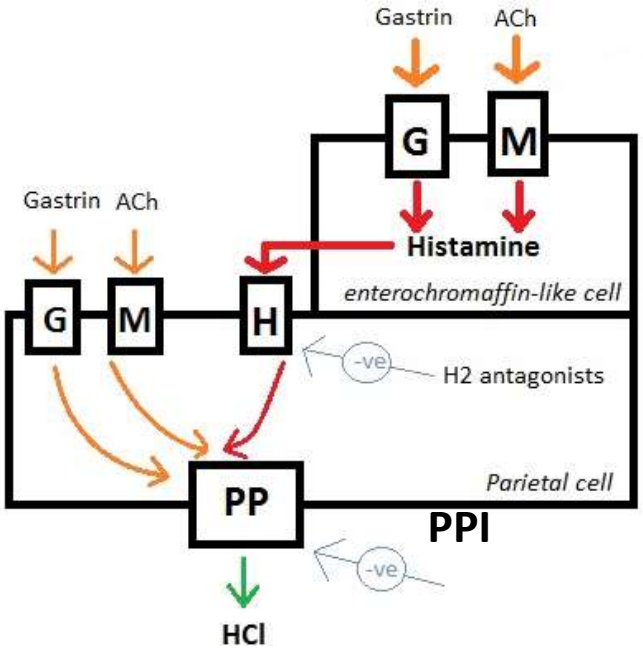
- CO_2 results in gastric distention and belching.

$NaHCO_3 + HCl \rightarrow NaCl + H_2O + \mathbf{CO_2}$

H2-Receptor Antagonists

Cimetidine, Ranitidine,

Famotidine Nizatidine.



Rapidly absorbed from intestine.

Cimetidine, ranitidine, famotidine

50 % first-pass metabolism bioavailability

Nizatidine has little first-pass metabolism.

Duration of action: 6–10 hours, given twice daily.

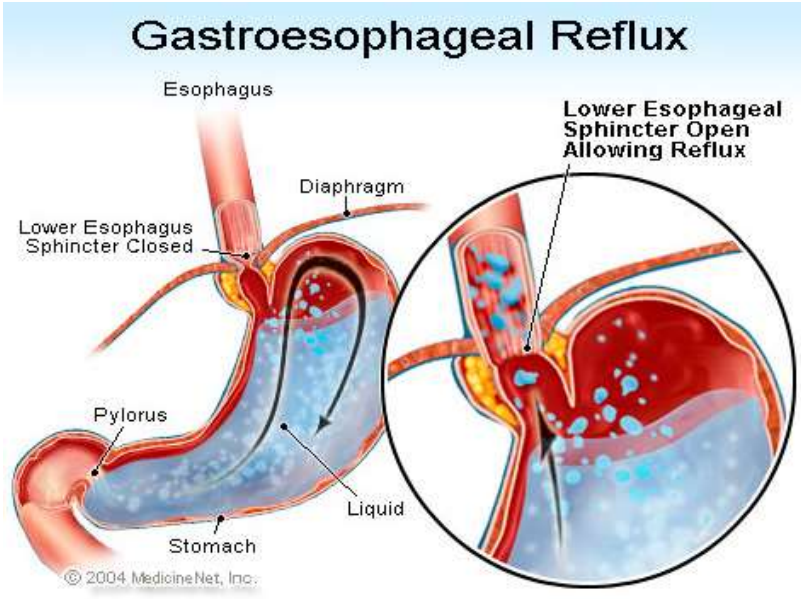
Inhibit 90% of nocturnal acid (depends on histamine).

Modest impact on meal-stimulated acid secretion (which is stimulated by gastrin, Ach and histamine).

Inhibit 60% of day-time, meal stimulated acid.

Inhibit 60-70% of total 24-h acid secretion.

Clinical Uses



Gastroesophageal Reflux Disease (GERD)

Taken prophylactically before meals.

In erosive esophagitis H2 antagonists healing is less than 50% hence **PPI** are preferred.

Non Ulcer Dyspepsia.

Over-the-counter agents for treatment of intermittent dyspepsia not caused by peptic ulcer.

Prevention of Bleeding from Stress-Related Gastritis

IV H2 antagonists are preferable over IV **PPI** because of their proven efficacy and lower cost.

Peptic Ulcer Disease:

Replaced by PPI.

Healing rate more than 80-90% after 6-8 wks.

Not effective in the presence of ***H. pylori.***

Not effective if NSAID is continued.

Adverse Effects:

Extremely safe drugs. Diarrhea, headache, fatigue, myalgias, and constipation (3%).

Cimetidine may cause gynecomastia & impotence in men (antiandrogenic effects) and galactorrhea in women

Drug Interactions:

Cimetidine inhibits cytochrome P450 enzymes so can increase half life of many drugs.

Ranitidine binds 4-10 times less.

Nizatidine and famotidine binding is negligible

Proton Pump Inhibitors (PPIs)

Among the most widely prescribed drugs worldwide due to their outstanding efficacy and safety.

Omeprazole (oral).

Lanzoprazole (oral and IV).

Esomeprazole (oral and IV).

available as capsules of enteric-coated granules.

Rabeprazole (oral).

Pantoprazole (oral and IV).

are tablets with a pH-sensitive coating.

Prodrugs, released in the intestine (Destroyed by acid).

Immediate-Release Omeprazole

contains sodium bicarbonate to protect the drug from acid degradation results in rapid response.

Lipophilic weak bases, absorbed in small intestine and delivered to parietal cell through the blood.

Drug is protonated and “trapped” in acidic canaliculi.

Concentrated more than 1000-fold in the parietal cells.

Converted to the active form which covalently binds the H+/K+ ATPase enzyme and inactivates it.

Have short half lives but effect lasts for 24 hours.

At least 18 hours are required for synthesis of new pump molecules.

Inhibit both fasting & meal-stimulated secretion

(90-98% of 24-hour secretion).

The full acid-inhibiting potential is reached in 3 to 4 days.