Clinical Uses of (PPIs) :

Gastroesophageal Reflux (GERD):

The most effective agents in all forms of GERD

Nonulcer Dyspepsia:

Modest activity.10-20% more beneficial than a placebo

Stress- Related Gastritis:

Oral immediate- release **omeprazole** administered by nasogastric tube.

For patients without a nasoenteric tube, **IV H_2- blockers** are preferred because of their proven efficacy.

Gastric acid hypersecretory states, including Zollinger -Ellison syndrome

Usually high doses of omeprazole are used.

Peptic Ulcer Disease:

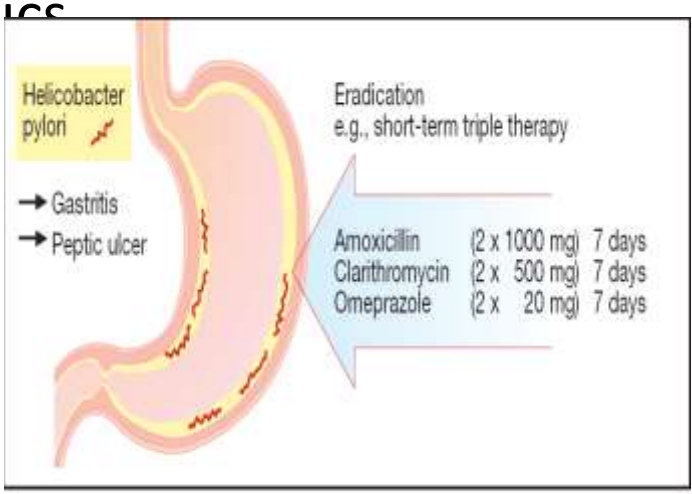
They heal more than 90% of cases within 4-6 weeks.

H. Pylori* - associated ulcers*:

PPI eradicate *H. pylori* by direct antimicrobial activity and by lowering MIC of the antibiotics.

***Triple Therapy*:**

PPI twice daily + Clarithromycin 500 mg twice daily +Amoxicillin 1gm twice daily ,OR, Metronidazole 500mg twice daily.



C. Helicobacter eradication

NSAID-associated ulcers*:*

Healing despite continued NSAID use.

Also used to prevent ulcer of NSAIDs

Rebleeding peptic ulcer:

Oral or IV. High pH may enhance coagulation and platelet aggregation.

Adverse Effects of PPIs:

Well tolerated.

May cause headache, diarrhea, abdominal pain, nausea & dizziness

Reduction of cyanocobalamine absorption.

Increased risk of GI and pulmonary infection.

Increased serum gastrin levels causes:

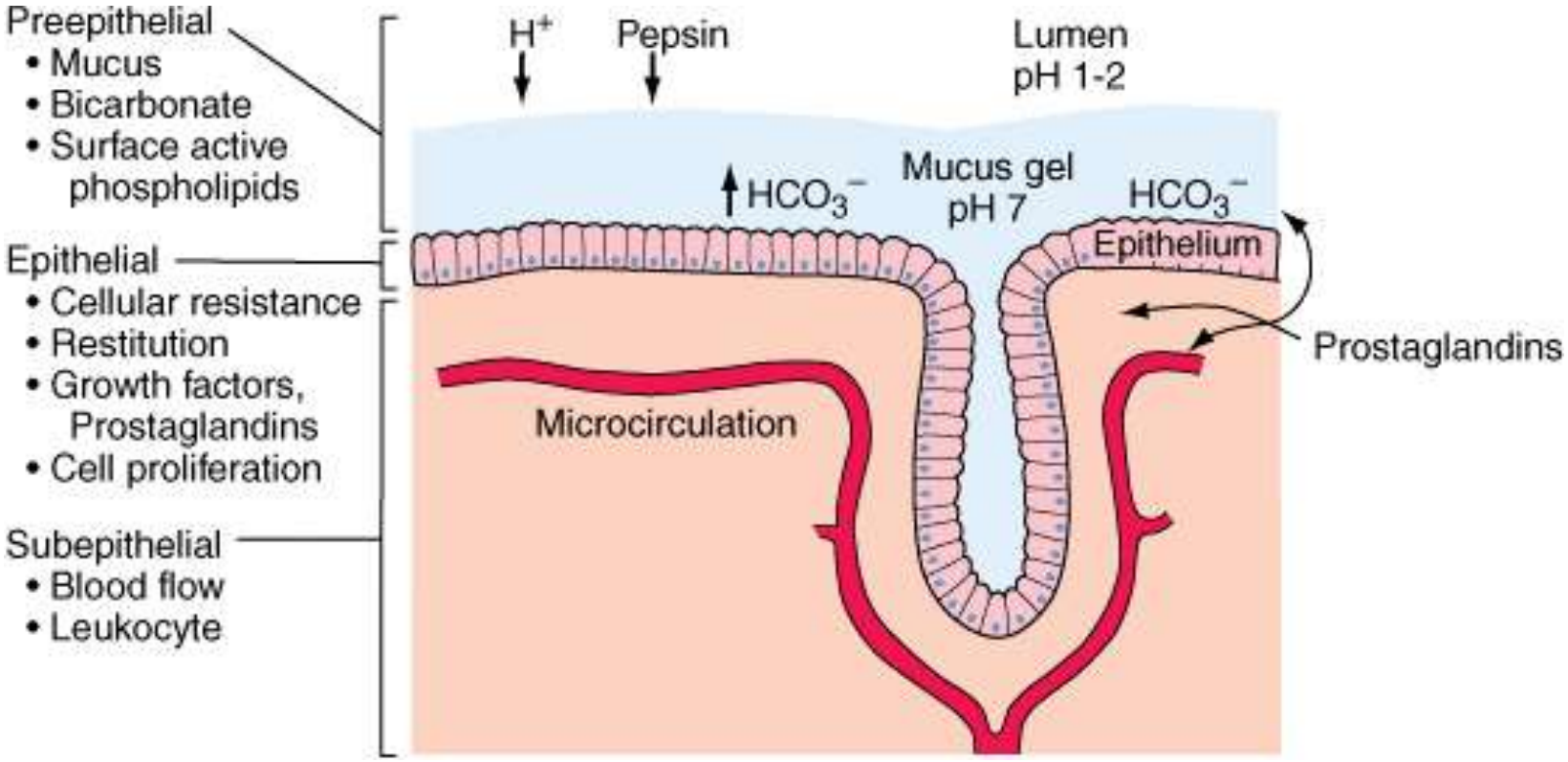
Chronic inflammation in gastric body.

Atrophic gastritis and intestinal metaplasia.

Drug Interactions:

May affect absorption of drugs due to decreased gastric acidity like digoxin and ketoconazole.

Mucosal Protective Agents



1-Both mucus and epithelial cell-cell tight junctions restrict back diffusion of acid and pepsin.

2-Epithelial bicarbonate secretion

3-Blood flow carries bicarbonate

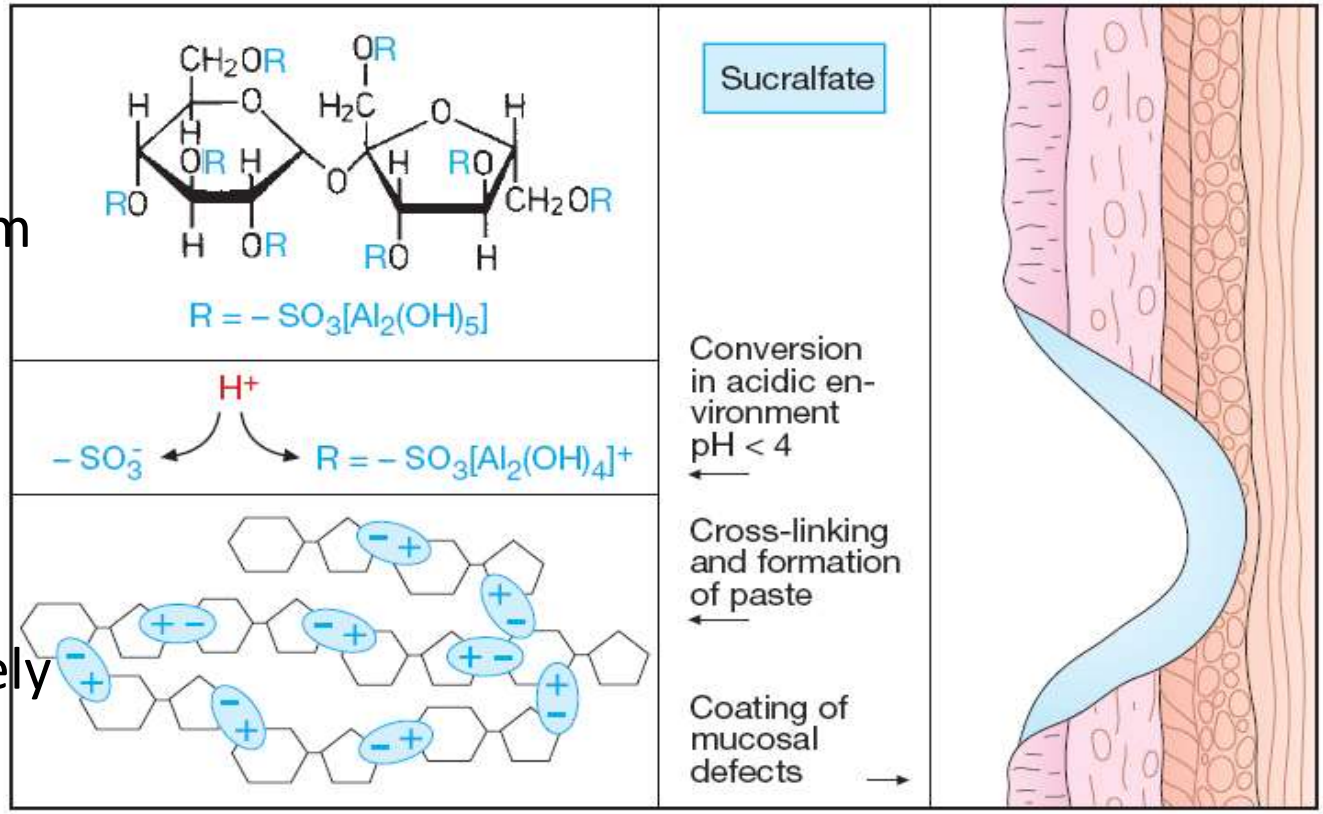
4- injured epithelium are repaired by **restitution**

5- Mucosal prostaglandins stimulates mucus and bicarbonate secretion and mucosal blood flow.

Sucralfate

A salt of sucrose complexed to sulfated aluminum hydroxide.

In the stomach, It breaks down into sucrose sulfate (strongly negatively charged) and an aluminum salt.



A. Chemical structure and protective effect of sucralfate

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**.

Acts for 6 hours.

Less than 3% of intact drug and aluminum is absorbed.

Clinical Uses

1 g four times daily on an empty stomach (through a nasogastric tube) reduces the incidence of upper GI bleeding in critically ill patients hospitalized in the intensive care unit.

Prevention of **stress-related bleeding** because acid inhibitory therapies may increase the risk of nosocomial pneumonia (an infection of the lungs that occurs during a **hospital** stay).

Adverse Effects

Not absorbed, so no systemic adverse effects.

Constipation (2%) due to the aluminum salt.

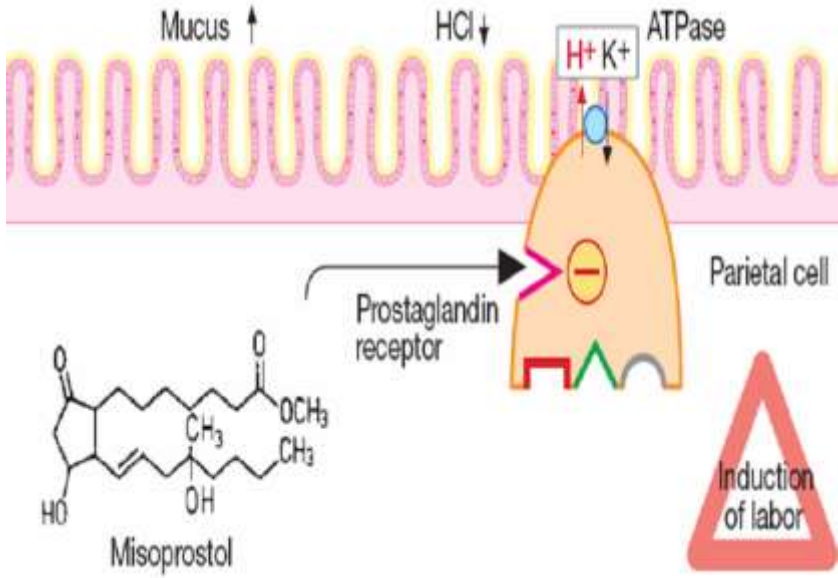
Caution in renal insufficiency.

Drug Interactions

Sucralfate may bind to other medications, impairing their absorption.

Prostaglandin Analogs

Misoprostol



A methyl analog of **PGE1.**

Half-life is less than 30 min

Administered 3-4 times daily.

1-Stimulates mucus
& bicarbonate secretion.

2- Enhances mucosal blood flow.

3- Acts on parietal cells, reducing histamine-stimulated cAMP production and causing **modest acid inhibition**.

4- Stimulates **intestinal** electrolyte & fluid secretion,

5- Increase intestinal motility

6- **Uterine contractions**.

Clinical Uses of Prostaglandin Analogs:

Prevention of NSAID-induced ulcers in high-risk patients.

Not widely used for this purpose because of:

a- side effects.

b. need for multiple daily dosing.

c. **PPI** may be as effective and better tolerated.

d. Cyclooxygenase2-selective NSAIDs are an option for such patients**.**

Adverse Effects & Drug Interactions

Diarrhea and cramping abdominal pain (10–20%).

it should not be used during pregnancy

No significant drug interactions.

Colloidal Bismuth Compounds:

Bismuth subsalicylate.

Bismuth subcitrate.

Bismuth is minimally absorbed from GIT (< 1%).

A mucosal protective agent, provides coat on the ulcer.

Reduce the gastric HCL secretion.

Help in eradication of H. pylori.

Stimulates the PGE secretion.

Reduce pepsin secretion.

Decrease H+ ion back diffusion.

Bismuth subsalicylate reduces stool frequency and liquidity in acute infectious diarrhea, due to salicylate inhibition of intestinal prostaglandin and chloride secretion.

Has direct antimicrobial effects & binds enterotoxins, so useful in preventing & treating **traveler's diarrhea**.

Widely used for the nonspecific treatment of dyspepsia and acute diarrhea.

Has direct antimicrobial activity against *H pylori and* used as second-line therapy for the eradication of *H pylori* infection

PPI with bismuth subsalicylate , tetracycline and metronidazole for 10–14 days).

Adverse Effects

Blackening of the stool and the tongue.

Prolonged usage may rarely lead to bismuth toxicity, resulting in **encephalopathy**.

Drugs Stimulating GI Motility

(**Prokinetic agents**)

Potential uses:

Increasing lower esophageal sphincter pressures, useful for GERD.

Improving gastric emptying, helpful for gastroparesis and postsurgical gastric emptying delay.

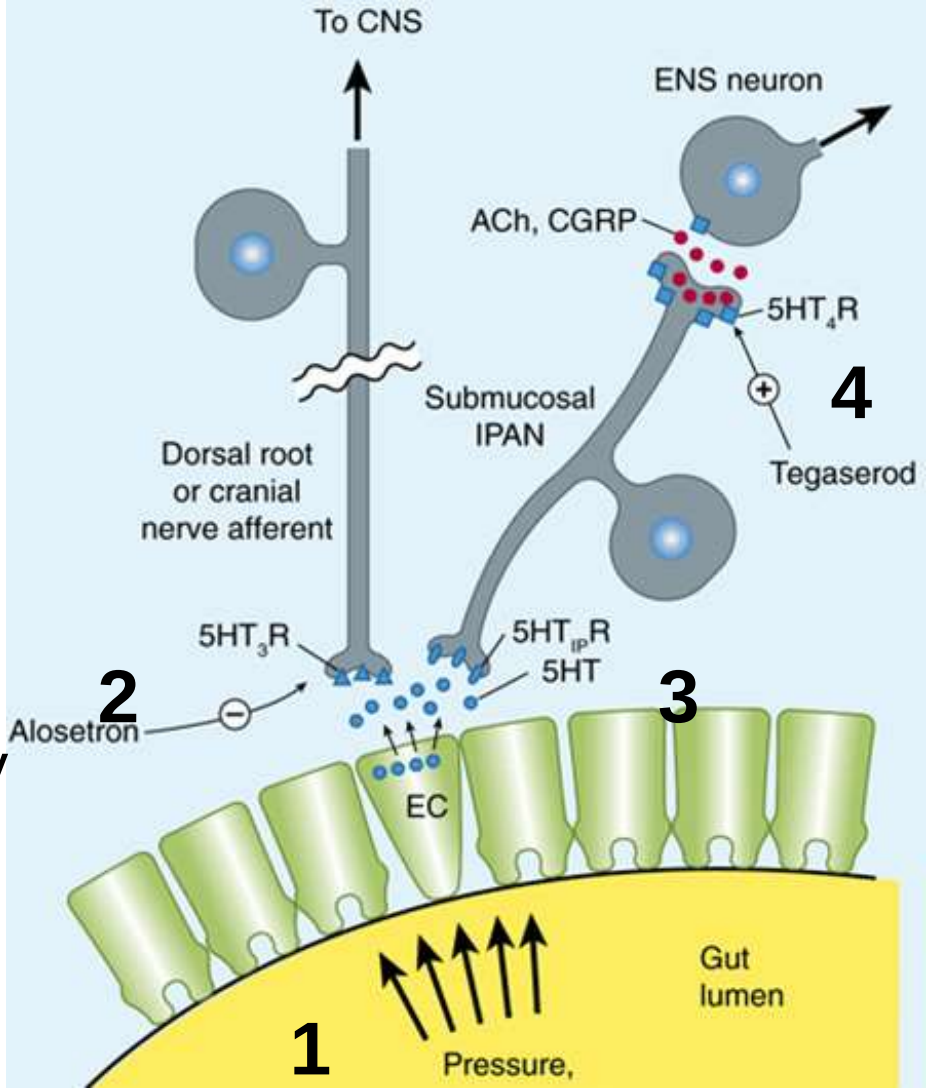
Stimulation of the small intestine useful for postoperative ileus.

Enhancing colonic transit, useful in the treatment of constipation.

1-Gut distention stimulates 5-HT release from EC cells.

2-Stimulation of **5-HT3** receptors on the extrinsic afferent nerves, stimulate **nausea, vomiting**, or **abdominal pain**.

3- 5-HT also stimulates **5-HT1P** receptors of the intrinsic primary afferent nerves (IPANs) which activate the enteric neurons responsible for **peristaltic and secretory reflex activity.**



4- Stimulation of 5-HT4 receptors (5-HT4R) on presynaptic terminals of IPANs enhances release of **ACh** & calcitonin gene related peptide (**CGRP**), promoting reflex activity.

The enteric nervous system can independently regulate GI motility and secretion.

The myenteric interneurons control:

peristaltic reflex, promoting release of excitatory mediators proximally and inhibitory mediators distally.

Motilin may stimulate excitatory neurons or muscle cells directly.

Dopamine acts as an inhibitory neurotransmitter in the GIT, decreasing the intensity of esophageal and gastric contractions.

Cholinomimetic Agents

Bethanechol

Stimulates muscarinic **M3** receptors on muscle cells and at myenteric plexus synapses .

Was used for the treatment of GERD and gastroparesis.

Neostigmine

AchE inhibitor enhances gastric, small intestine, and colonic emptying.

IV neostigmine used for the treatment of acute large bowel distention (**acute colonic pseudo-obstruction**).

Administration of 2 mg results in prompt colonic evacuation of flatus and feces.

Cholinergic effects include excessive salivation, nausea, vomiting, diarrhea, and bradycardia.

Dopamine D2-receptor antagonists.

Metoclopramide & Domperidone

D2 Antagonists.

Dopamine acts as an inhibitory neurotransmitter in the GIT, decreasing the intensity of esophageal & gastric contractions.

These agents block D2 receptors causing:

-increase esophageal peristaltic amplitude.

-increase lower esophageal sphincter pressure.

-enhance gastric emptying.

-have no effect on small intestine or colonic motility.

Also block dopamine **D2** receptors in the **chemoreceptor trigger zone of the medulla (area postrema),** resulting in potent **anti nausea and antiemetic actions.**

Clinical Uses

Gastroesophageal Reflux Disease

Not effective with **erosive esophagitis**.

Not superior to antisecretory agents.

Used mainly in combination with antisecretory agents in patients with **refractory heartburn**.

Impaired Gastric Emptying (Gastroparesis)

widely used in post surgical and diabetic gastroparesis

Nonulcer Dyspepsia

Prevention of Vomiting

Postpartum Lactation Stimulation.

Domperidone is used to promote postpartum lactation.

Adverse Effects:

Metclopromide crosses BBB so can cause:

Restlessness, drowsiness, insomnia, anxiety, agitation, extrapyramidal symptoms (dystonia, akathisia, parkinsonian features) and tardive dyskinesia.

Domperidone does not cross the BBB, so

does not cause CNS effects

Both drugs can elevate serum prolactin levels causing galactorrhea, gynecomastia, impotence and menstrual disorders.