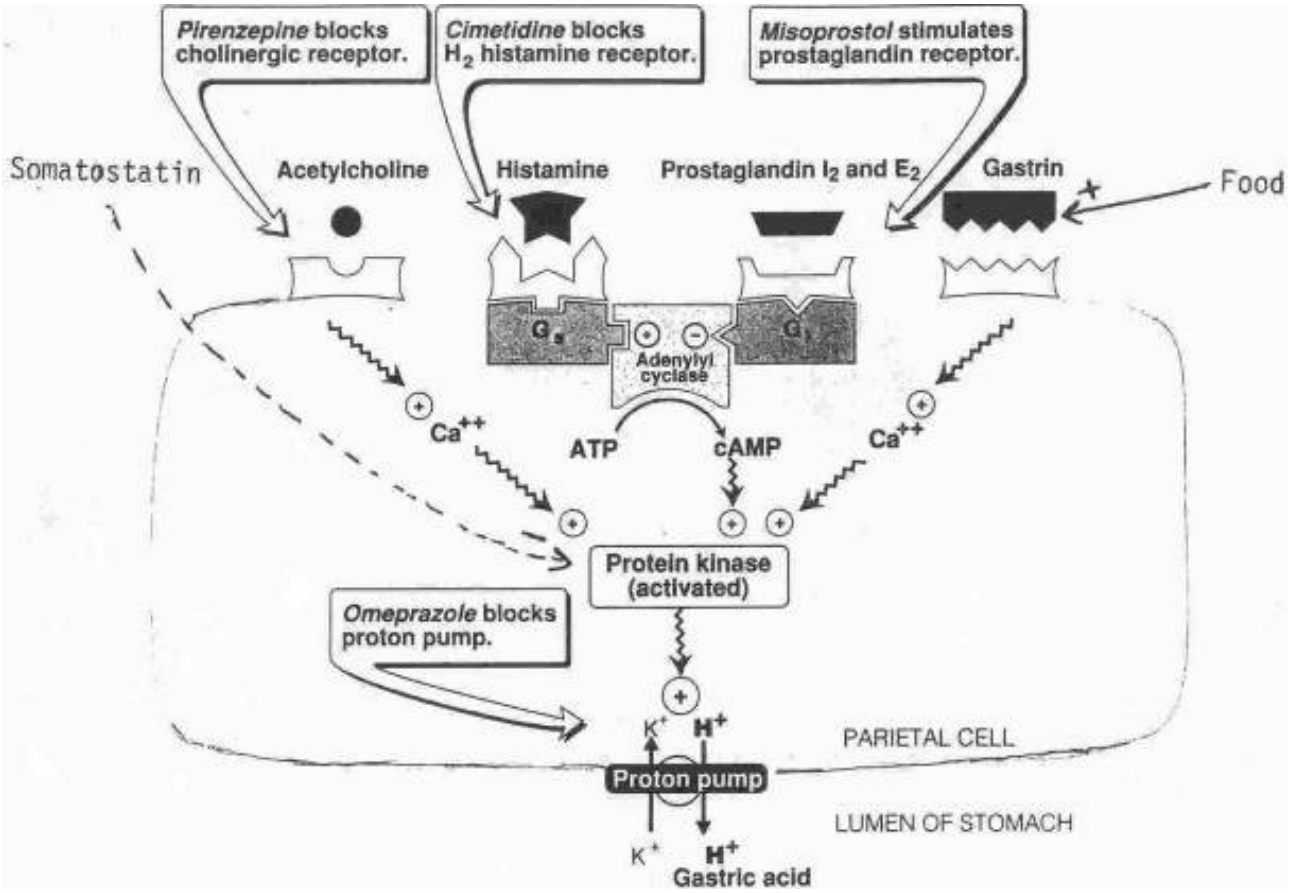
DRUGS USED FOR PEPTIC ULCER DISEASE

Definition: A peptic ulcer, also known as PUD or peptic ulcer disease, is an ulcer defined as mucosal erosions equal to or greater than 0.5 cm^2 of an area of the gastrointestinal tract that is usually acidic which is extremely painful.

Pathophysiology:



Simply, it is thought that an imbalance between aggressive factors (e.g. acid and pepsin) and defensive factors (e.g. mucus and bicarbonate secretion, prostaglandins, etc) exists in patients suffering from PUD. However, nowadays, it seems that the H. pylori infection theory is important.

Objectives of treatment: pain relief, healing of ulcer, prevention of further ulcer recurrance.

Objectives accomplished by:
1. Inhibiting the aggressive factors
2. Enhancing mucosal resistance
3. Eradication of H.Pylori

Classification of drugs for peptic ulcer:
1. Drugs that reduce intragastric acidity
2. Mucosal protective agents

Drugs That Decrease Intragastric Acidity

Antacids

These are mainly inorganic salts e.g. $NaHCO_3$, $CaCO_3$, $Al(OH)_3$, and $Mg(OH)_2$

Mechanism of action:
They chemically react with the gastric hydrochloric acid forming neutral products. They may also decrease pepsin's activity indirectly.

Gaviscon® is a drug combination of alginic acid and $NaHCO_3$

Constituent	Neutralizing Capacity	Salt Formed in Stomach	solubility of Salt	Adverse Effects
$NaHCO_3$	High	NaCl	High	Systemic alkalosis, fluid retention Gastric distention
$CaCO_3$	Moderate	$CaCl_2$	Moderate	Hypercalcemia, nephrolithiasis, milk-alkali syndrome*
$Al(OH)_{3**}$	High	$AlCl_3$	Low	Constipation, hypophosphatemia, drug adsorption reduces bioavailability
$Mg(OH)_{2**}$	High	$MgCl_2$	Low	Diarrhea, hypermagnesemia (in patients with renal insufficiency

*Excessive doses of calcium carbonate with calcium containing dairy products can lead to hypercalcemia, renal insufficiency, and metabolic alkalosis (milk-alkali syndrome)

**These agents are commonly administered together in proprietary formulations

All antacids affect the absorption of other medications by binding the drug or by increasing intragastric pH so that the drug's dissolution or solubility is altered (should not be given within 2 hours of doses of tetracyclines, fluoroquinolones, itraconazole, and iron).

H_2-Receptor Antagonists

- Examples: Cimetidine, Ranitidine, Famotidine, and Nizatidine

Mechanism of Action:
They block histamine's action on the H2 receptor which plays a major role on parietal cell proton pump activation.

Potency VS Efficacy: Ranitidine is more potent than cimetidine on the H2 receptor. Therefore, it is given less frequently and in smaller doses. Cimetidine is considered more efficacious as an H2 blocker.

Pharmacokinetics: all four agents are rapidly absorbed from the intestine. Cimetidine, ranitidine, and famotidine undergo first-pass metabolism. They are cleared by hepatic metabolism, glomerular filtration, renal tubular secretion. Doses are reduced in renal or hepatic impairment

Side Effects and Drug Interactions: Cimetidine is considered to be an antiandrogenic drug causing gynecomastia and impotence in males and galactorrhea in females. Cimetidine is also a well-known hepatic enzyme inhibitor, leading to the prolongation of many microsome enzyme-dependent drugs. Ranitidine rarely causes leukopenia and blood dyscriasis.

Anticholinergics (pirenzipine)

They are not used anymore because of the limited effect of ACH on inducing gastric acid secretion.

Proton pump inhibitors

Examples: Omeprazole, Lansoprazole, Pantoprazole, Raperazole

MOA: are potent inhibitors of the H^+-K^+ ATPase pump. This enzyme, located in the apical secretory membrane of the parietal cell, plays a key role in the secretion of H^+ (protons).

Pharmacokinetics:
All are available in oral formulations. Lansoprazole and pantoprazole are available in IV formulations. Drugs should be administered on an empty stomach so that the peak serum concentration coincides with the maximal activity of proton pump secretion. They undergo hepatic metabolism and dose reduction is considered in patients with severe liver impairment.

▶ What is the effect of combining H2-Blockers or antiacids with PPIs?

An antagonistic effect. PPIs are considered prodrugs which are reabsorbed in the small intestine then trasnported to the parietal cells in the stomach to be protonated into the active form. H2 blockers inhibit the pumping of free protons into parietal cells, hence preventing PPI activation.

Clinical Uses: Gastric and duodenal ulcers due to H.Pylori, Zollinger–Ellison syndrome (gastrinoma), GERD, and NSAIDs induced ulceration **.**

Side Effects: Headache, diarrhea, nausea, decrease gastric acid secretion alters normal feedback inhibition with a rise in gastrin median levels (hypergastrinemia) and mucosal hyperplasia.

Mucosal Protective Agents
Sucralfate

Contains Aluminum and Disaccharide

Pharmacokinetics: In acidic solutions it forms a paste that binds selectively to ulcers. 3% of the drug is absorbed the remainder is excreted in the feces.

Adverse Effects: Constipation, nausea/vomiting, and back pain.

Bismuth subsalicylate

Pharmacokinetics: undergoes rapid dissociation within the stomach, allowing absorption of salicylates. Bismuth appears in the stool. Salicylates is excreted in the urine

Pharmacodynamics: bismuth coats ulcers. Also, it has antidiarrheal and antimicrobial activity.

Adverse Effects: blackening of the stool, darkening of the tongue by liquid formulations, high dosage may lead to salicylate toxicity. Should be avoided in patients with renal insufficiency.

Prostaglandin (Misoprostol)

Pharmacokinetics: Oral administration. Metabolized to the active free acid. It is excreted in the urine.

Pharmacodynamics: it has two actions: stimulates mucus and bicarbonate excretion and reduces histamine-stimulated acid production

Adverse Effects: Diarrhea and cramping abdominal pain. Avoided in pregnancy and in case of childbearing women there has to be a negative pregnancy test.

Clinical pharmacology of drugs used in peptic ulcer: eradication of H. Pylori by omeprazole, amoxicillin, and clarithromycin; Rx of Zollinger-Ellison; Rx of NSAIDs induced peptic ulcer; Rx GERD.