Drugs that Control Gastric Acid Secretion and Treat Peptic Ulcers

The introduction of antisecretory compounds, firstly histamine (H2) receptor antagonists and then proton pump inhibitors (PPIs), has led to the reduction of surgical intervention.

Physiology of gastric secretion

Gastric acid secretion originates with an energy-requiring hydrolysis of water into hydrogen and hydroxyl ions in oxyntic (parietal) cells. The hydrogen ions, as well as chloride ions, are actively secreted into the stomach lumen to form hydrochloric acid. Gastric acid aids digestion by creating the optimal pH for pepsin and gastric lipase and by stimulating pancreatic bicarbonate secretion.

Regulation of acid secretion

Acid secretion can be regulated by three major pathways:

- neural stimulation via the vagus nerve,
- endocrine stimulation via gastrin released from antral G cells
- paracrine stimulation by the local release of histamine from enterochromaffin-like cells.

Normally, the GI mucosa is protected by several distinct mechanisms:

- Mucosal production of thick viscid mucus and HCO3 creates.
- Epithelial cells tight junctions.
- Mucosal blood flow removes excess acid that has diffused across the epithelial layer.

Several growth factors (eg, epidermal growth factor, insulin-like growth factor I) and prostaglandins have been linked to mucosal repair and maintenance of mucosal integrity.

Factors that interfere with these mucosal defenses

- NSAIDs reduce gastric blood flow, reduce mucus and HCO3 secretion, and decrease cell repair and replication.
- Helicobacter pylori infection.

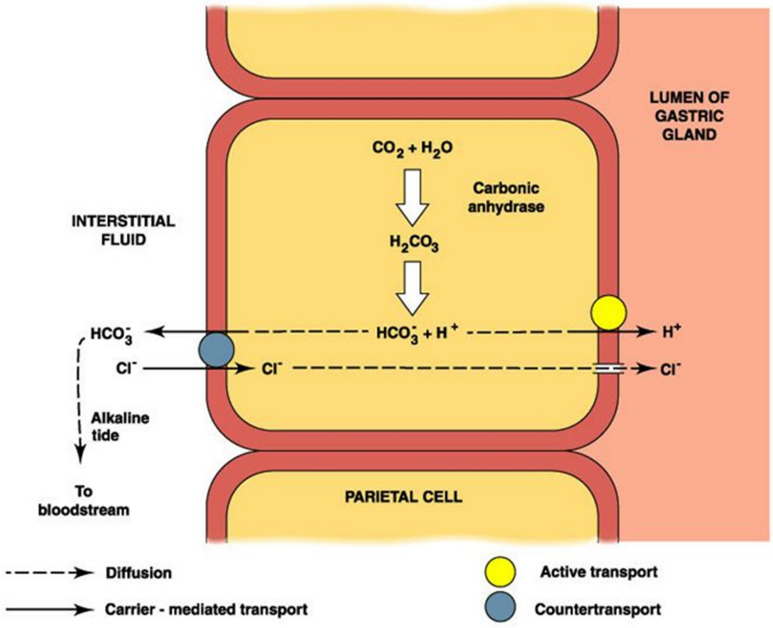

Figure: gastric acid secretion.

1.Antacids

The famous theory “no acid, no ulcer” of the early years of the past century, led to the identification of this class of drugs during the 60’s. The principal target of this class of drugs is the neutralization of the acid secreted by parietal cells, maintaining the pH of the stomach at values greater than or equal to 4. The antacid composition varies with constituents and acid-neutralizing capability. The most common are hydroxide of magnesium and aluminum but also sodium bicarbonate and calcium carbonate are used as well.

2.Histamine (H2) Receptor Antagonists

Histamine has two types of receptors: H1 and H2. Activation of H1 receptors produces the classic symptoms of inflammation and allergy, whereas the H2 receptors are responsible for increasing acid secretion in the stomach. The H2-receptor antagonists are effective at suppressing the volume and acidity of parietal cell secretions, by selectively binding and blocking H2 receptors in the stomach. The main H2-receptor antagonists are

- cimetidine,
- ranitidine,
- famotidine,
- nizatidine .

Indications:

- Short-Term Treatment of Active Duodenal Ulcer
- Maintenance Therapy for Duodenal Ulcer Patients at Reduced Dosage after Healing of Active Ulcer
- Short-Term Treatment of Active Benign Gastric Ulcer
- Erosive Gastroesophageal Reflux Disease (GERD) (Oral Solution Only)
- Prevention of Upper Gastrointestinal Bleeding in Critically Ill Patients (Injection Only)
- The Treatment of Pathological Hypersecretory Conditions: (i.e., Zollinger-Ellison Syndrome).

Side effect: Diarrhea, constipation, headache, fatigue, nausea, gynecomastia

3.Proton Pump Inhibitors (PPIs)

The agonist (histamine, acetylcholine or gastrin) interacting with their own receptor leads to the activation of the H+/K+ ATPase pump, which is able to increase the hydrogen ions into the lumen. The proton pump inhibitors act by selective blocking of H+/K+ ATPase pump, thus decrease gastric acid secretion. The main Proton Pump Inhibitors (PPIs)are

Omeprazole is the first of a class of drugs, Four additional PPIs are now available: *dexlansoprazole ,lansoprazole, rabeprazole , pantoprazole, and esomeprazole*.

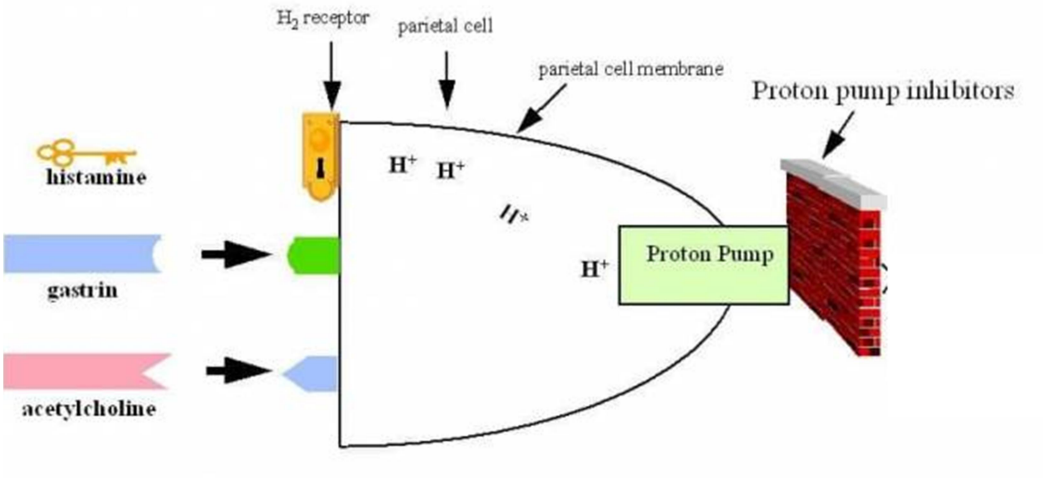

Figure: mechanism of action of Proton Pump Inhibitors (PPIs)

Therapeutic uses:

1. PPIs reduce the risk of bleeding from an ulcer caused by aspirin and other NSAIDs.
2.They are used with antimicrobial regimens to eradicate H. pylori.
3.For stress ulcer treatment and prophylaxis
4.The treatment of GERD, erosive esophagitis, active duodenal ulcer,
5.Zollinger-Ellison syndrome.

Side effect: Headache, dizziness diarrhea, nausea, rash, anemia.
Increased risk for osteoporosis-related fractures of the hip, wrist, or spine

Pharmacotherapy to eradicate H. pylori

The gram-negative bacterium H. pylori is associated with 80% of patients with duodenal ulcers and 70% of those with gastric ulcers. It is also strongly associated with gastric cancer.

A combination of antibiotics is used concurrently to eradicate H. pylori. Example regimens used to eradicate H. pylori include the following:

- Initial regimen: Omeprazole, clarithromycin (Biaxin), and amoxicillin (Amoxil, others).
- Alternative regimens: Omeprazole, clarithromycin and metronidazole (Flagyl),
- or Omeprazole, bismuth subsalicylate (Pepto-Bismol), metronidazole (Flagyl), and tetracycline.

Miscellaneous Drugs

for Peptic Ulcer Disease Several additional drugs are beneficial in treating PUD.

1.Sucralfate (Carafate) consists of sucrose (a sugar) plus aluminum hydroxide (an antacid). The drug produces a thick, gel-like substance that coats the ulcer, protecting it against further erosion and promoting healing. A major disadvantage of sucralfate is that it must be taken four times daily.

2.Misoprostol (Cytotec)

Prostaglandin E2, produced by the gastric mucosa, inhibits secretion of HCl and stimulates secretion of mucus and bicarbonate . A deficiency of prostaglandins is thought to be involved in the pathogenesis of peptic ulcers. Misoprostol , a stable analog of prostaglandin E1. Prophylactic use of misoprostol should be considered

in patients who are taking NSAIDs, such as elderly patients and those with previous ulcers. Misoprostol produces uterine contractions and is contraindicated during pregnancy. Dose-related diarrhea and nausea are the most common adverse effects.

F. Antimuscarinic agents

Muscarinic receptor stimulation increases gastrointestinal motility and secretory activity. dicyclomine, can be used as an adjunct in the management of peptic ulcer disease. Side effects (cardiac arrhythmias, dry mouth, constipation, and urinary retention) limit its use

Constipation

As waste material travels through the large intestine, water is reabsorbed. Reabsorption of the proper amount of water results in stools of a normal, soft-formed consistency. If the waste material remains in the colon for an extended period, however, too much water will be reabsorbed, leading to small, hard stools. Constipation may cause abdominal distention and discomfort and flatulence. Constipation is not a disease but a symptom of an underlying disorder. The etiology of constipation may be related to lack of exercise; insufficient food intake, especially insoluble dietary fiber; diminished fluid intake; or a medication regimen that includes drugs that reduce intestinal motility. Opioids, anticholinergics, antihistamines, certain antacids.

Laxatives

Laxatives are commonly used to accelerate the movement of food through the gastrointestinal tract.

Classifications

A. stimulants laxatives

- Senna is a widely used stimulant laxative.
- Bisacodyl: available as suppositories and enteric-coated tablets, is a potent stimulant of the colon.
- Castor oil

B. Bulk laxatives

The bulk laxatives include

- hydrophilic colloids, they form gels in the large intestine, causing water retention and intestinal distension, thereby increasing peristaltic activity.
- methylcellulose,
- psyllium seeds

- bran for chronic constipation.

C. Saline and Osmotic laxatives

- magnesium citrate
- sodium phosphate,

are nonabsorbable salts (anions and cations) that hold water in the intestine by osmosis increasing intestinal activity and producing defecation.

D. Stool softeners (emollient laxatives or surfactants)

These include

- docusate sodium,
- docusate calcium
- docusate potassium. They may take days to become effective and are often used for prophylaxis rather than acute treatment.

E. Lubricant laxatives

Mineral oil and glycerin suppositories are considered to be lubricants. They facilitate the passage of hard stools.

F. Chloride channel activators

Lubiprostone works by activating chloride channels to increase fluid secretion in the intestinal lumen. This eases the passage of stools and causes little change in electrolyte balances.

Diarrhea

Diarrhea may be caused by

- certain medications,
- infections of the bowel, and substances such as lactose.
- Inflammatory disorders such as ulcerative colitis, Crohn's disease
- Irritable bowel syndrome (IBS)
- Antibiotics often cause diarrhea by killing normal intestinal flora.

The primary goal in treating diarrhea is to assess and treat the underlying condition causing the diarrhea and replace body fluid loss specially in children.

Antidiarrheals

Increased motility of the gastrointestinal tract and decreased absorption of fluid are major factors in diarrhea. Antidiarrheal drugs include antimotility agents, adsorbents, and drugs that modify fluid and electrolyte transport.

A. Antimotility agents

Diphenoxylate and loperamide Both are analogs of meperidine and opioid-like actions on the gut, activating presynaptic opioid receptors in the enteric nervous system to inhibit acetylcholine release and decrease peristalsis . Side effects include drowsiness, abdominal cramps, and dizziness. they should not be used in young children or in patients with severe colitis.

B. Adsorbents

Methylcellulose and aluminum hydroxide these agents act by adsorbing intestinal toxins or microorganisms and/or by coating or protecting the intestinal mucosa. Kaolin and pectin increase viscosity of the gut contents and adsorb bacteria and toxins. They are much less effective than antimotility agents and they can interfere with the absorption of other drugs.

C. Agents that modify fluid and electrolyte transport

Bismuth subsalicylate, used for traveler's diarrhea, decreases fluid secretion in the bowel. Its action may be due to its salicylate component as well as its coating action. Adverse effects may include black tongue and black stools.

Side effect:

- Drowsiness, light-headedness, nausea, dizziness,
- Dry mouth (from atropine), constipation
- Paralytic ileus with toxic megacolon,
- Respiratory depression,
- central nervous system (CNS) depression

NAUSEA AND VOMITING

Nausea is an unpleasant, subjective sensation that is accompanied by weakness, diaphoresis, and hyperproduction of saliva. It is sometimes accompanied by dizziness. Intense nausea often leads to vomiting, or emesis. Vomiting is a defense mechanism used by the body to rid itself of toxic substances. Vomiting is a reflex primarily controlled by the vomiting center of the medulla of the brain, which

receives sensory signals from the digestive tract, the inner ear, and the chemoreceptor trigger zone (CTZ) in the cerebral cortex.

Note: Emetic actions of chemotherapeutic agents

Chemotherapeutic agents (or their metabolites) can directly activate the medullary chemoreceptor trigger zone or vomiting center; several neuroreceptors, including dopamine receptor Type 2 and serotonin Type 3 (5-HT3) from cell damage(GIT and pharynx) play roles in vomiting.

Antiemetic drugs

1. Anticholinergic drugs: especially the muscarinic receptor antagonist, scopolamine, and H1-receptor antagonists(diphenhydramine) are very useful in motion sickness but are ineffective against substances that act directly on the chemoreceptor trigger zone.

2.Phenothiazines and Butyrophenones: Droperidol, haloperidol and phenothiazines are antipsychotic agents that effective antiemetic and sedative properties such as prochlorperazine act by blocking dopamine receptors and is effective against low or moderately emetogenic chemotherapeutic agents. adverse reactions include extrapyramidal symptoms and sedation. Droperidol had been used most often for sedation in endoscopy and surgery, usually in combination with opioids or benzodiazepines.

3. Serotonin receptor blockers: This class of agents an important place in treating emesis linked with chemotherapy because of their longer duration of action and superior efficacy. These drugs can be administered as a single dose prior to chemotherapy (intravenously or orally) and are efficacious against all grades of emetogenic therapy. The specific antagonists of the 5-HT3 receptor ondansetron selectively block 5-HT3 receptors in the periphery and in the brain. Headache and Electrocardiographic changes are most common side effect.

4. Metoclopramide acts by blocking dopamine D2 receptors in the CTZ and peripherally , is effective at high doses. Antidopaminergic side effects, including sedation, diarrhea, and extrapyramidal symptoms, limit its high-dose use. Domperidone is a selective D2 receptor antagonist.

5. Benzodiazepines: The antiemetic potency of lorazepam and alprazolam is low. Their beneficial effects may be due to their sedative, anxiolytic, and amnesic properties.

6.Corticosteroids: Dexamethasone and methylprednisolone , used alone, are effective against mildly to moderately emetogenic chemotherapy. Their antiemetic mechanism is not known, but it may involve blockade of prostaglandins.

7. Combination therapy: dexamethasone and ondansetron. Dexamethasone, diphenhydramine, metoclopramide and droperidol. Lorazepam, dexamethasone and metoclopramide. Diphenhydramine, dexamethasone and metoclopramide.