Gastrointestinal and Antiemetic Drugs

Part 1

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Drugs used to treat peptic ulcer disease and gastroesophageal reflux disease

- 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.

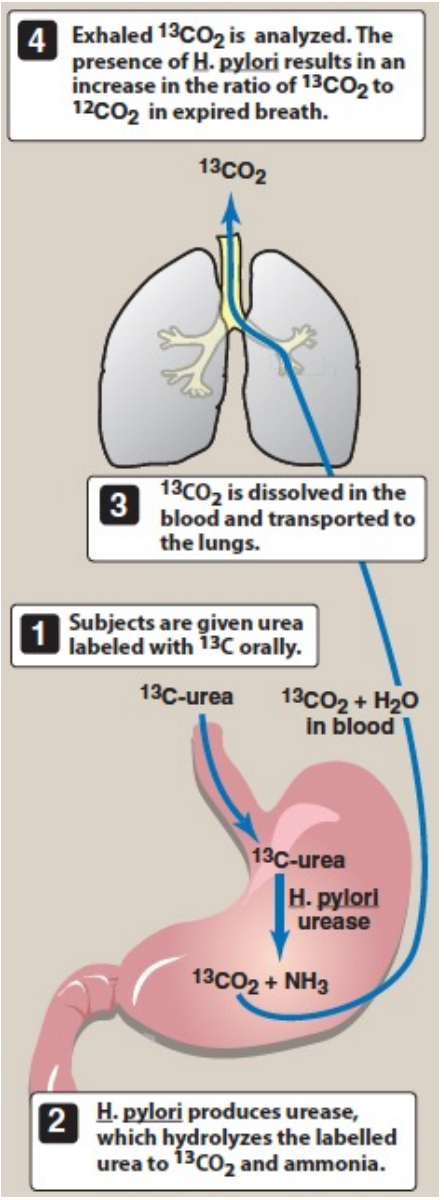
- Treatment approaches include 1) eradicating the H. pylori infection, 2) reducing secretion of gastric acid with the use of PPIs or H2-receptor antagonists, and/or 3) providing agents that protect the gastric mucosa from damage, such as misoprostol and sucralfate.

A. Antimicrobial agents

- Patients with peptic ulcer disease (duodenal or gastric ulcers) who are infected with H. pylori require antimicrobial treatment.

- Infection with H. pylori is diagnosed via endoscopic biopsy of the gastric mucosa or various noninvasive methods, including serology and urea breath tests.

- Eradication of H. pylori results in rapid healing of active ulcers and low recurrence rates (less than 15% compared with 60% to 100% per year for initial ulcers healed with acid-reducing therapy alone). Successful eradication of H. pylori (80% to 90%) is possible with various combinations of antimicrobial drugs.



A. Antimicrobial agents

- Currently, **triple therapy** consisting of a **PPI** combined with **amoxicillin** (**metronidazole** may be used in penicillin-allergic patients) plus **clarithromycin** is the therapy of choice.

- **Quadruple therapy** of **bismuth subsalicylate, metronidazole, and tetracycline plus a PPI** is another option. Quadruple therapy should be considered in areas with high resistance to clarithromycin. This usually results in a 90% or greater eradication rate. Treatment with a single antimicrobial drug is much less effective, results in antimicrobial resistance, and is not recommended.

- Substitution of antibiotics is also not recommended (that is, do not substitute ampicillin for amoxicillin or doxycycline for tetracycline).

- GERD (heartburn) is not associated with H. pylori infection and does not respond to antibiotics.

B. H_2-receptor antagonists and regulation of gastric acid secretion

- Gastric acid secretion is stimulated by acetylcholine, histamine, and gastrin. The receptor-mediated binding of acetylcholine, histamine, or gastrin results in the activation of protein kinases, which in turn stimulates the H^+/K^+-adenosine triphosphatase (ATPase) proton pump to secrete hydrogen ions in exchange for K^+ into the lumen of the stomach. By competitively blocking the binding of histamine to H_2 receptors, these agents reduce the secretion of gastric acid.

- ***Ranitidine, famotidine, and nizatidine*** potently inhibit (greater than 90%) basal, food-stimulated, and nocturnal secretion of gastric acid.

- **Actions:** The histamine H_2-receptor antagonists act selectively on H_2 receptors in the stomach, but they have no effect on H_1 receptors. They are competitive antagonists of histamine and are fully reversible.

B. H_2-receptor antagonists and regulation of gastric acid secretion

- **Therapeutic uses:** The use of these agents has decreased with the advent of PPIs.

a. Peptic ulcers: All four agents are equally effective in promoting the healing of duodenal and gastric ulcers. However, recurrence is common if H. pylori is present and the patient is treated with these agents alone.

- Patients with NSAID-induced ulcers should be treated with PPIs, because these agents heal and prevent future ulcers more effectively than H_2 antagonists do.

b. Acute stress ulcers: These drugs are given as an intravenous infusion to prevent and manage acute stress ulcers associated with high-risk patients in intensive care units. However, because tolerance may occur with these agents in this setting, PPIs have gained favor for this indication.

c. Gastroesophageal reflux disease (GERD): Low doses of H_2 antagonists, currently available for over-the-counter sale, are effective for the treatment of heartburn (GERD) in only about 50% of patients. H_2-receptor antagonists act by stopping acid secretion. Therefore, they may not relieve symptoms for at least 45 minutes.

- Antacids more quickly and efficiently neutralize stomach acid, but their action is only temporary. For these reasons, PPIs are now used preferentially in the treatment of GERD, especially for patients with severe heartburn.

C. PPIs: 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***.

- ***Omeprazole, esomeprazole, and lansoprazole*** are available over-the counter for short-term treatment of GERD.

- **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 over the counter and by prescription.

C. PPIs: Inhibitors of the H^+/K^+-ATPase proton pump

- **Therapeutic uses:** The PPIs are superior to the H_2 antagonists in suppressing acid production and healing ulcers. Thus, they are the preferred drugs for stress ulcer treatment and prophylaxis and for the treatment of GERD, erosive esophagitis, active duodenal ulcer, and pathologic hypersecretory conditions (for example, Zollinger-Ellison syndrome, in which a gastrin-producing tumor causes hypersecretion of HCl).

- If a once-daily PPI is only partially effective for GERD symptoms, increasing dosing to twice daily or administering the PPI in the morning and adding an H_2 antagonist in the evening may improve symptom control. If an H_2-receptor antagonist is needed, it should be taken well after the PPI.

- H_2 antagonists reduce the activity of the proton pump, and PPIs require active pumps to be effective. PPIs also 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.

C. PPIs: Inhibitors of the H^+/K^+-ATPase proton pump

- **Pharmacokinetics:** All of 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.

- **Esomeprazole, lansoprazole, and pantoprazole** are also available in intravenous formulations.

- **Side effects:** ***Omeprazole and esomeprazole*** may decrease the effectiveness of clopidogrel because they inhibit CYP2C19 and prevent the conversion of clopidogrel to its active metabolite.

- Although the effect on clinical outcomes is questionable, concomitant use of these PPIs with clopidogrel is not recommended because of a possible increased risk of cardiovascular events.

D. 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.

- Prophylactic use of misoprostol should be considered in patients who are taking NSAIDs and are at moderate to high risk of NSAID-induced ulcers, such as elderly patients and those with previous ulcers.

- Misoprostol is contraindicated in pregnancy, since it can stimulate uterine contractions and cause miscarriage.

- Dose-related diarrhea and nausea are the most common adverse effects and limit the use of this agent. Thus, PPIs are preferred agents for the prevention of NSAID-induced ulcers.

E. Antacids

- Antacids are weak bases that react with gastric acid to form water and a salt to diminish gastric acidity. Because pepsin (a proteolytic enzyme) is inactive at a pH greater than 4, antacids also reduce pepsin activity.

- **Chemistry:** Antacid products vary widely in their chemical composition, acid-neutralizing capacity, sodium content, palatability, and price. The efficacy of an antacid depends on its capacity to neutralize gastric HCl and on whether the stomach is full or empty (food delays stomach emptying allowing more time for the antacid to react).

- Commonly used antacids are combinations of salts of aluminum and magnesium, such as aluminum hydroxide and magnesium hydroxide [$Mg(OH)_2$]. Calcium carbonate [$CaCO_3$] reacts with HCl to form CO2 and CaCl2 and is also a commonly used preparation.

- Systemic absorption of sodium bicarbonate [NaHCO3] can produce transient metabolic alkalosis. Therefore, this antacid is not recommended for long-term use.

- **Therapeutic uses:** Antacids are used for symptomatic relief of peptic ulcer disease and GERD, and they may also promote healing of duodenal ulcers.

- They should be administered after meals for maximum effectiveness.

F. Mucosal protective agents

- Also known as cytoprotective compounds, these agents have several actions that enhance mucosal protection mechanisms, thereby preventing mucosal injury, reducing inflammation, and healing existing ulcers.

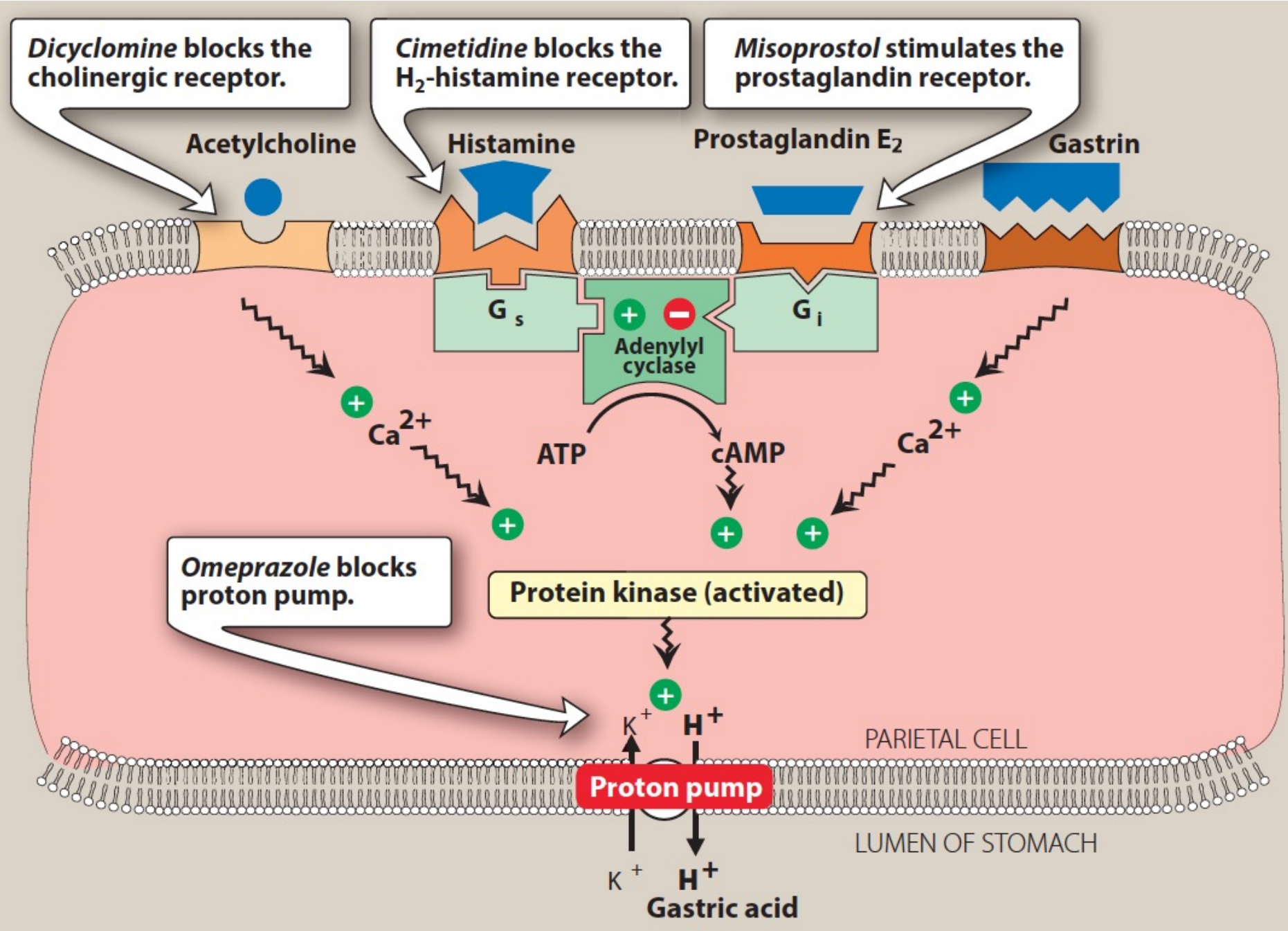
1. ***Sucralfate:*** This complex of aluminum hydroxide and sulfated sucrose binds to positively charged groups in proteins of both normal and necrotic mucosa. By forming complex gels with epithelial cells, sucralfate creates a physical barrier that protects the ulcer from pepsin and acid, allowing the 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 and drug–drug interactions.

- Because it requires an acidic pH for activation, sucralfate should not be administered with PPIs, H_2 antagonists, or antacids.

- This agent does not prevent NSAID-induced ulcers, and it does not heal gastric ulcers.

2. ***Bismuth subsalicylate:*** This agent is used as a component of quadruple therapy to heal peptic ulcers. In addition to its antimicrobial actions, it inhibits the activity of pepsin, increases secretion of mucus, and interacts with glycoproteins in necrotic mucosal tissue to coat and protect the ulcer.


Dicyclomine blocks the cholinergic receptor.
Cimetidine 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


Thank You!