Drugs acting on Gastrointestinal tract

Drugs that used to treat three common medical conditions involving the gastrointestinal tract: peptic ulcers and gastroesophageal reflux disease (GERD), chemotherapy-induced emesis, and diarrhea and constipation.

**Drugs Used to Treat Peptic Ulcer Disease**

Several major causative factors are: nonsteroidal anti-inflammatory drug (NSAID) use, infection with gram-negative Helicobacter pylori, increased hydrochloric acid secretion, and inadequate mucosal defense against gastric acid. Treatment approaches include 1) eradicating the H. pylori infection, 2) reducing secretion of gastric acid with the use of H2-receptor antagonists or PPIs, and/or 3) providing agents that protect the gastric mucosa from damage, such as misoprostol and Sucralfate.

**A. Antimicrobial agents**

Optimal therapy for patients with peptic ulcer disease (both duodenal and gastric ulcers) who are infected with H. pylori requires 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. Currently, either triple therapy consisting of a PPI with either metronidazole or amoxicillin plus clarithromycin, or quadruple therapy of bismuth subsalicylate and metronidazole plus tetracycline plus a PPI, are administered for a 2-week course.

**B. Regulation of gastric acid secretion**

Gastric acid secretion by parietal cells of the gastric mucosa 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. In contrast, receptor binding of prostaglandin E2 diminishes gastric acid production.

**C. H2-receptor antagonists**

Although antagonists of the histamine H2 receptor block the actions of histamine at all H2 receptors, their chief clinical use is to inhibit gastric acid secretion, being particularly effective against nocturnal acid secretion at bedtime (which depends largely on histamine). By competitively blocking the binding of histamine to H2 receptors. The four drugs cimetidine, ranitidine, famotidine, and nizatidine.

**Actions:** The histamine H2-receptor antagonists drugs act selectively on H2 receptors in the stomach, blood vessels, and other sites, but they have no effect on H1 receptors (in skin). They are competitive antagonists of histamine and are fully reversible.

- **Therapeutic uses:**
  - Duodenal and gastric ulcers, recurrence is common if H. pylori is present and the patient is treated with these agents alone
  - Acute stress ulcers: drugs are given as an intravenous infusion (except nizatidine) to prevent and manage acute stress ulcers and tolerance may occur
  - Gastroesophageal reflux disease: (heartburn) Low doses of H2 antagonists, they may not relieve symptoms for at least 45 minutes.

- **Pharmacokinetics:**
  - Cimetidine: Cimetidine t1/2(2hr) and the other H2 antagonists are given orally and I.V daily doses 800mg. Cimetidine inhibits cytochrome P450 isoenzymes and slow metabolism (potentiate the
action) of several drugs (for example, warfarin, diazepam, phenytoin, quinidine, carbamazepine, theophylline, and imipramine, sometimes resulting in serious adverse clinical effects.

- Ranitidine (1/2(2hr)): Compared to cimetidine, ranitidine is longer acting and is five- to ten-fold more potent. Ranitidine daily doses 300mg has minimal side effects and does not produce the antiandrogenic or prolactin-stimulating effects of cimetidine.
- Famotidine: Famotidine is similar to ranitidine in its pharmacologic action, but it is 20 to 50 times more potent than cimetidine, and 3 to 20 times more potent than ranitidine.
- Nizatidine: Nizatidine is similar to ranitidine in its pharmacologic action and potency. In contrast to cimetidine, ranitidine, and famotidine, which are metabolized by the liver, nizatidine is eliminated principally by the kidney.

- Adverse effects: headache, dizziness, diarrhea, and muscular pain. Other central nervous system effects (confusion, hallucinations) occur primarily in elderly patients or after intravenous administration, gynecomastia, galactorrhea (continuous release/discharge of milk) in cimetidine.

D. Inhibitors of the H+/K+-ATPase proton pump

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

- **Actions**: These 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 form, which reacts with a cysteine residue of the H+/K+-ATPase, forming a stable covalent bond. It takes about 18 hours for the enzyme to be resynthesized. Acid suppression begins within 1 to 2 hours after the first dose of lansoprazole and slightly earlier with omeprazole. There is also an oral product containing omeprazole combined with sodium bicarbonate for faster absorption.
- **Therapeutic uses**: healing peptic ulcers

1. PPIs reduce the risk of bleeding from an ulcer caused by aspirin and other NSAIDs.
2. They are also successfully 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, in which a gastrin-producing tumor causes hypersecretion of HCl).

- **Pharmacokinetics**: All these agents are delayed-release formulations, half-life 1.5hrs and are effective orally. For maximum effect, PPIs should be taken 30 minutes before breakfast or the largest meal of the day. If an H2-receptor antagonist is also needed, it should be taken well after the PPI for best effect. H2 antagonists reduce the activity of the proton pump, and PPIs require active pumps to be effective. Metabolites of these agents are excreted in urine and feaces.
**Adverse effects**: nausea, diarrhea, headache, GI disturbance and Bone Fractures (increased risk with long-term (1 year or greater) use: hip, wrist, and spine.

**E. Prostaglandins**
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.

**G. Antacids**
Antacids are weak bases that react with gastric acid to form water and a salt, thereby diminishing gastric acidity. Because pepsin is inactive at a pH greater than 4, antacids also reduce pepsin activity.

**Actions**: Antacids more quickly and efficiently neutralize stomach acid, but their action is only temporary and on whether the stomach is full or empty (food delays stomach emptying allowing more time for the antacid to react). Calcium carbonate [CaCO3] reacts with HCl to form CO2 and CaCl2 and is also a commonly used preparation.

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

**Adverse effects**: Aluminum hydroxide tends to be constipating, and magnesium hydroxide tends to produce diarrhea. Preparations that combine these agents aid in normalizing bowel function.

**H. Mucosal protective agents**
cytoprotective compounds, these agents have several actions that enhance mucosal protection mechanisms, thereby preventing mucosal injury, reducing inflammation, and healing existing ulcers.

**Sucralfate**: This complex of aluminum hydroxide and sulfated sucrose. By forming complex gels with epithelial cells, Sucralfate creates a physical barrier that impairs diffusion of HCl and prevents degradation of mucus by pepsin and acid. 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.

**Bismuth subsalicylate**: Antimicrobial actions, inhibits the activity of pepsin, increases secretion of mucus, and interacts with glycoproteins in necrotic mucosal tissue to coat and protect the ulcer.
**Emesis** (vomiting)

nausea and vomiting may occur in a variety of conditions (for example, motion sickness, pregnancy, or hepatitis) and are always unpleasant for the patient.

**A. Mechanisms that trigger vomiting**

Two brainstem sites have key roles in the vomiting reflex pathway. The chemoreceptor trigger zone, which is located in the outside of blood-brain barrier. The second important site, the vomiting center, which is located in the lateral reticular formation of the medulla, coordinates the motor mechanisms of vomiting. The vestibular system functions mainly in motion sickness.

**B. 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.

**C. 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.

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.

Antidiarrheal

Increased motility of the gastrointestinal tract and decreased absorption of fluid are major factors in diarrhea. Antidiarrheal drugs include antimitility 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 antimitility 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.

Laxatives

Laxatives are commonly used to accelerate the movement of food through the gastrointestinal tract. These drugs can be classified on the basis of their mechanism of action. They may also cause electrolyte imbalances when used chronically. Many of these drugs have a risk of dependency for the user.

Classifications

A. stimulants laxatives

Senna is a widely used stimulant laxative. Its active ingredient is a group of sennosides, a natural complex of anthraquinone glycosides. Taken orally, it causes evacuation of the bowels within 8 to 10 hours. It also causes water and electrolyte secretion into the bowel.

Bisacodyl: available as suppositories and enteric-coated tablets, is a potent stimulant of the colon. It acts directly on nerve fibers in the mucosa of the colon.

Castor oil: This agent is broken down in the small intestine to ricinoleic acid, which is very irritating to the stomach and promptly increases peristalsis. Pregnant patients should avoid castor oil because it may stimulate uterine contractions.

B. Bulk laxatives

The bulk laxatives include hydrophilic colloids (from indigestible parts of fruits and vegetables). They form gels in the large intestine, causing water retention and intestinal distension, thereby increasing peristaltic activity. Similar actions are produced by methylcellulose, psyllium seeds, and bran for chronic constipation.

C. Saline and Osmotic laxatives

magnesium citrate, sodium phosphate, and magnesium hydroxide, are nonabsorbable salts (anions and cations) that hold water in the intestine by osmosis.
and distend the bowel, increasing intestinal activity and producing defecation in a few hours. **Lactulose** is a semisynthetic disaccharide sugar that also acts as an osmotic laxative. It is a product that cannot be hydrolyzed by intestinal enzymes. Oral doses are degraded in the colon by colonic bacteria into lactic, formic, and acetic acids. This increases osmotic pressure, causing fluid accumulation, colon distension, soft stools, and defecation. Lactulose is also used for the treatment of hepatic encephalopathy, due to its ability to reduce ammonia levels. Electrolyte solutions containing **polyethylene glycol** (PEG) are used as colonic lavage solutions to prepare the gut for radiologic or endoscopic procedures.

**D. Stool softeners (emollient laxatives or surfactants)**

Surface-active agents that become emulsified with the stool produce softer feces and ease passage. These include **docusate sodium, docusate calcium, and 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. Nausea is a relatively common side effect with lubiprostone.