➢ Gastrointestinal and antiemetic drugs

Lecture 12

College of Pharmacy

By:

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➢ Gastrointestinal and antiemetic drugs

- Common medical conditions involving the gastrointestinal (GI) tract:

1) peptic ulcers and gastroesophageal reflux disease (GERD), 2) chemotherapy-induced emesis, 3) diarrhea, 4) constipation, 5) irritable bowel syndrome (IBS), and 6) and inflammatory bowel disease (IBD).

❖ 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

✓ The use of nonsteroidal anti-inflammatory drugs (NSAIDs).

Increased hydrochloric acid (HCl) 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 PPIs or H2 receptor antagonists, and/or 3) providing agents that protect the gastric mucosa from damage, such as misoprostol and sucralfate.

ANTIMICROBIAL AGENTS

Amoxicillin GENERIC ONLY
Bismuth compounds PEPTO-BISMOL, KAOPECTATE
Clarithromycin BIAXIN
Metronidazole FLAGYL
Tetracycline GENERIC ONLY

H_2 – HISTAMINE RECEPTOR BLOCKERS

Cimetidine TAGAMET
Famotidine PEPCID
Nizatidine AXID
Ranitidine ZANTAC

PROTON PUMP INHIBITORS

Dexlansoprazole DEXILANT
Esomeprazole NEXIUM
Lansoprazole PREVACID
Omeprazole PRILOSEC
Pantoprazole PROTONIX
Rabeprazole ACIPHEX

PROSTAGLANDINS

Misoprostol CYTOTEC

ANTIMUSCARINIC AGENTS

Dicyclomine BENTYL

ANTACIDS

Aluminum hydroxide GENERIC ONLY
Calcium carbonate TUMS
Magnesium hydroxide MILK OF MAGNESIA
Sodium bicarbonate ALKA-SELTZER

MUCOSAL PROTECTIVE AGENTS

Bismuth subsalicylate PEPTO-BISMOL
Sucralfate CARAFATE

Figure 1: Summary of drugs used to treat peptic ulcer disease

A. Antimicrobial agents

- Patients with peptic ulcer disease who are infected with H. pylori require antimicrobial treatment.
- Eradication of H. pylori with various combinations of antimicrobial drugs results in rapid healing of active ulcers and low recurrence.
- Currently, quadruple therapy of bismuth subsalicylate, metronidazole, and tetracycline plus a PPI is a recommended first-line option.
- Triple therapy consisting of a PPI combined with amoxicillin (metronidazole may be used in penicillin-allergic patients) plus clarithromycin.

B. H2 receptor antagonists

See figure (2). The four drugs used in the United States—**cimetidine, famotidine, nizatidine, and ranitidine**—inhibit basal, food-stimulated, and nocturnal secretion of gastric acid, reducing acid secretion by approximately 70%.

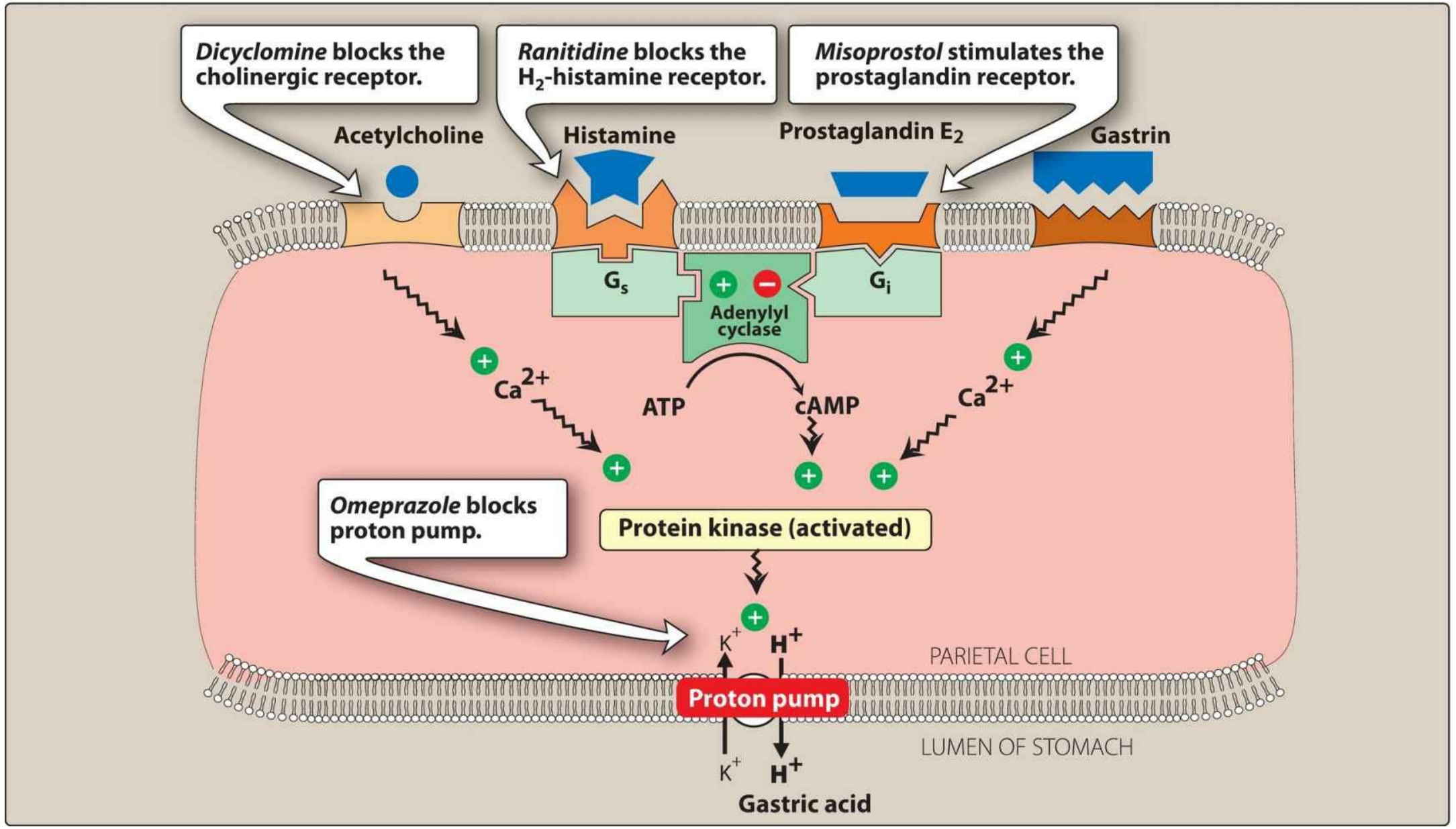

Figure 2: Effects of acetylcholine, histamine, prostaglandin E2, and gastrin on gastric acid secretion by the parietal cells of stomach. Gs and Gi are membrane proteins that mediate the stimulatory or inhibitory effect of receptor coupling to adenylyl cyclase.

Therapeutic uses

a. Peptic ulcers b. Acute stress ulcers c. Gastroesophageal reflux disease

Pharmacokinetics

- After oral administration, the H2 receptor antagonists distribute widely throughout the body (including into breast milk and across the placenta) and are excreted mainly in the urine.
- The half-life of these agents may be increased in patients with renal dysfunction, and dosage adjustments are needed.

Adverse effects

- Cimetidine can have endocrine effects, such as gynecomastia and galactorrhea (continuous release/discharge of milk), because it acts as a nonsteroidal antiandrogen.
- Other central nervous system effects such as confusion and altered mentation occur primarily in elderly patients and after intravenous administration.
- Drug interaction could also occur.

C. 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.**

- 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.
- An oral product containing omeprazole combined with sodium bicarbonate for faster absorption is also available.

Therapeutic uses

- They are the preferred drugs for the treatment of GERD, erosive esophagitis, active duodenal ulcer, and pathologic hypersecretory conditions such as Zollinger-Ellison syndrome.
- PPIs 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.
- PPIs are also used for stress ulcer prophylaxis and management.
- Finally, PPIs are combined with antimicrobial regimens used to eradicate H. pylori.

Pharmacokinetics

- 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 available in intravenous formulations.

- Although the plasma half-life of these agents is only a few hours, they have a long duration of actioncovalent bonding with the H^+/K^+-ATPase enzyme. .
- Metabolites of these agents are excreted in urine and feces.

Adverse effects

- PPIs may increase the risk of fractures, particularly if the duration of use is 1 year or greater.
- Prolonged acid suppression with PPIs (and H2 receptor antagonists) may result in low vitamin B12.
- Elevated gastric pH may also impair the absorption of calcium carbonate.
- Diarrhea and Clostridium difficile colitis may occur in patients receiving PPIs. Patients must be counseled to discontinue PPI therapy and contact their physician if they have diarrhea for several days.
- Additional adverse effects may include hypomagnesemia and an increased incidence of pneumonia.
- Drug interaction could also occur.

D. Prostaglandins

- Prostaglandin E, produced by the gastric mucosa, inhibits secretion of acid and stimulates secretion of mucus and bicarbonate.
- **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 take 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 is the most common adverse effect and limits the use of this agent.

E. Antacids

- Antacids are weak bases that react with gastric acid to form water and a salt to diminish gastric acidity.
- 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 and prolonging the duration of action.
- Commonly used antacids are combinations of salts of aluminum and magnesium, such as **aluminum hydroxide and magnesium hydroxide.**
- Calcium carbonate reacts with HCl to form CO2 and CaCl2 and is also a commonly used preparation.

Therapeutic uses

Antacids are used for symptomatic relief of peptic ulcer disease, heartburn, and GERD. They should be administered after meals for maximum effectiveness.

Adverse effects

- Aluminum hydroxide tends to cause constipation, whereas magnesium hydroxide tends to produce diarrhea.
- Preparations that combine these agents aid in normalizing bowel function. Accumulation and adverse effects may occur in patients with renal impairment.

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. It 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, drug–drug interactions, and availability of more effective agents.

2. Bismuth subsalicylate

This agent is used as a component of quadruple therapy to heal H. pylori-related 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.

Drugs Used to Control Chemotherapy-Induced Nausea and Vomiting (CINV)

- The nausea and vomiting produced by chemotherapeutic agents demands especially effective management.
- Factors influence the incidence and severity of CINV, including:

The specific chemotherapeutic drug; the dose, route, and schedule of administration; and patient variables.

Mechanisms that trigger vomiting

Two brainstem sites have key roles in the vomiting reflex pathway:

- The chemoreceptor trigger zone (CTZ) is located in the area postrema
- The second important site, the vomiting center, which is located in the lateral reticular formation of the medulla, coordinates the motor mechanisms of vomiting.

Emetic actions of chemotherapeutic agents

- Chemotherapeutic agents can directly activate the medullary CTZ or vomiting center. Several neuroreceptors, including dopamine receptor type 2 and serotonin type 3 (5-HT_3), play critical roles.
- Chemotherapeutic drugs can also act peripherally by causing cell damage in the GI tract and by releasing serotonin from the enterochromaffin cells of the small intestine.

Antiemetic drugs

1- Phenothiazines

Phenothiazines, such as prochlorperazine act by blocking dopamine receptors in the CTZ. It is effective against low or moderately emetogenic chemotherapeutic agents (for example, fluorouracil and doxorubicin).

2. 5-HT_3 receptor blockers

- The 5-HT_3 receptor antagonists include **dolasetron, granisetron, ondansetron, and palonosetron**.
- These agents selectively block 5-HT_3 receptors in the periphery and in the CTZ.
- This class of agents is important in treating CINV, because of their superior efficacy and longer duration of action.
- These drugs can be administered as a single dose prior to chemotherapy (intravenously or orally); and they are also useful in the management of postoperative nausea and vomiting.
- 5-HT_3 antagonists are extensively metabolized by the liver; however, only ondansetron requires dosage adjustments in hepatic insufficiency. Excretion is via the urine.

3. Substituted benzamides

- **Metoclopramide** is effective at high doses against the emetogenic cisplatin.
- Metoclopramide accomplishes this through inhibition of dopamine in the CTZ.

- Antidopaminergic adverse effects, including extrapyramidal symptoms, limit long-term high-dose use.
- Metoclopramide enhances gastric motility and is useful for patients with gastroparesis.

4. Butyrophenones

- **Droperidol** and haloperidol act by blocking dopamine receptors.
- These agents are moderately effective antiemetics.
- Droperidol had been used most often for sedation in endoscopy and surgery, usually in combination with opioids or benzodiazepines.

5. Benzodiazepines

- The antiemetic potency of lorazepam and alprazolam is low.
- Their beneficial effects may be due to their sedative, anxiolytic, and amnestic properties.
- Concomitant use of alcohol should be avoided due to additive CNS depressant effects.

6. Corticosteroids

- **Dexamethasone and methylprednisolone**, used alone, are effective against mildly to moderately emetogenic chemotherapy. Most frequently, they are used in combination with other agents. It may involve blockade of prostaglandins.

7. Substance P/neurokinin-1 receptor antagonists

- **Aprepitant, netupitant, and rolapitant** target the neurokinin receptor in the vomiting center and block the actions of substance P.

- These oral agents are indicated for highly or moderately emetogenic chemotherapy regimens, they are effective for the delayed phase of CINV, which occurs 24 hours or more after chemotherapy, these agents are usually administered with dexamethasone and a 5-HT_3 antagonist.
- Fatigue, diarrhea, abdominal pain, and hiccups are adverse effects of this class.

8. Combination regimens

- Antiemetic drugs are often combined to increase efficacy or decrease toxicity. See figure 3

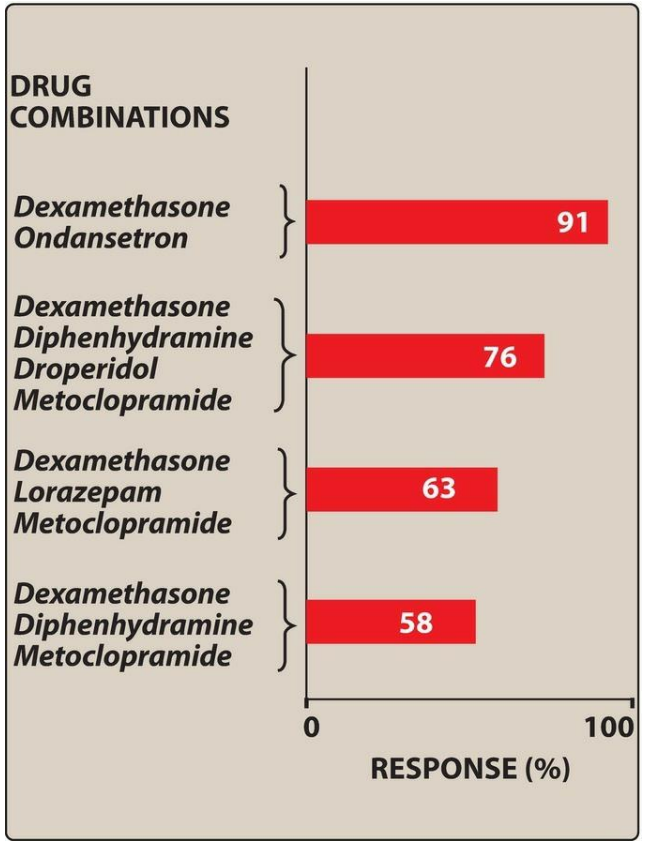

Figure 3: Effectiveness of antiemetic activity of some drug combinations against emetic episodes in the first 24 hours after cisplatin chemotherapy.

Antidiarrheals

- Increased motility of the GI 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

- Two drugs that are widely used to control diarrhea are **diphenoxylate and loperamide.**
- Both have opioid-like actions on the gut; they activate presynaptic opioid receptors in the enteric nervous system to inhibit acetylcholine release and decrease peristalsis.

- Loperamide is used for the general treatment of acute diarrhea, including traveler's diarrhea.
- Because these drugs can contribute to toxic megacolon, they should not be used in young children or in patients with severe colitis.

B. Adsorbents

Adsorbent agents, such as **aluminum hydroxide and methylcellulose**, are used to control diarrhea. Presumably, these agents act by adsorbing intestinal toxins or microorganisms and/or by coating or protecting the intestinal mucosa. 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 prevention and treatment of 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 in the treatment of constipation to accelerate the motility of the bowel, soften the stool, and increase the frequency of bowel movements.
- Laxatives increase the potential for loss of pharmacologic effect of poorly absorbed, delayed-acting, and extended-release oral preparations by accelerating their transit through the intestines.

- They may also cause electrolyte imbalances when used chronically.
- Many of these drugs have a risk of dependency for the user.

A. Irritants and stimulants

1. Senna

This agent is a widely used stimulant laxative. Taken orally, senna causes evacuation of the bowels within 6 to 12 hours. It also causes water and electrolyte secretion into the bowel. In combination products with a docusate-containing stool softener, it is useful in treating opioid-induced constipation.

2. Bisacodyl

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

3. 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. Use of castor oil is generally not recommended due to poor palatability and potential for GI adverse effects.

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. Similar actions are produced by methylcellulose, psyllium seeds, and bran. They should be used cautiously in patients who are immobile because of their potential for causing intestinal obstruction. Psyllium can reduce the absorption of other oral drugs, and administration of other agents should be separated from psyllium by at least two hours.

C. Saline and osmotic laxatives

Saline cathartics, such as **magnesium citrate and magnesium hydroxide**, are nonabsorbable salts that hold water in the intestine by osmosis. This distends the bowel, increasing intestinal activity and producing defecation in a few hours.

D. Stool softeners

Surface active agents that become emulsified with the stool produce softer feces and ease passage of stool. These include **docusate sodium and docusate calcium**. 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 lubricants and act by facilitating the passage of hard stools. Mineral oil should be taken orally in an upright position to avoid its aspiration and potential for lipid or lipoid pneumonia.

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 balance.

Irritable Bowel Syndrome

- Irritable bowel syndrome (IBS) is characterized by chronic abdominal pain and altered bowel habits in the absence of an organic cause.
- IBS may be classified as constipation predominant (IBS-C), diarrhea predominant (IBS-D), or a combination of both.
- Key characteristics of medications used for the treatment of IBS-C and IBS-D are provided in Figure 4.

DRUG	INDICATION	MECHANISM OF ACTION	ADVERSE EFFECTS
Linaclotide	IBS-C*	Increases intestinal fluid secretion via increased cGMP	Diarrhea, abdominal pain, flatulence, and abdominal distention Do not use in children < 17 years old
Lubiprostone	Women with IBS-C*	Chloride channel activator	Nausea and vomiting, dyspepsia, headache, dizziness, and hypotension
Alosetron	Women with severe IBS-D	5-HT_3 antagonist	Constipation, nausea and vomiting, heartburn, ischemic colitis (rare)
Eluxadoline	IBS-D	μ-Opioid receptor agonist	Constipation, abdominal pain, nausea, pancreatitis (rare) Possible risk of dependence and overdose
Rifaximin	Short-term use in IBS-D	Decreases bacterial load (structural analog of *rifampin*)	Nausea, fatigue, headache, dizziness, peripheral edema, and risk of Clostridium difficile infection
Dicyclomine	IBS-C and IBS-D	Antimuscarinic; decreases GI spasms and motility	Anticholinergic effects such as drowsiness and dry mouth
Hyoscyamine	IBS-C and IBS-D	Antimuscarinic; decreases GI spasms and motility	Anticholinergic effects such as drowsiness and dry mouth Overdose may produce hallucinations, arrhythmias, and nausea and vomiting

Figure 4: Characteristics of drugs used to treat irritable bowel syndrome. cGMP = cyclic guanosine monophosphate; IBS-C = irritable bowel syndrome with constipation; IBS-D = irritable bowel syndrome with diarrhea; GI = gastrointestinal. *Also indicated for the treatment of chronic constipation.

Drugs Used to Treat Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is a group of idiopathic chronic intestinal conditions characterized by immunemediated GI tract inflammation in response to bacterial antigens in the intestinal lumen.

The most common subtypes of IBD are **Crohn's disease (CD) and ulcerative colitis (UC).**

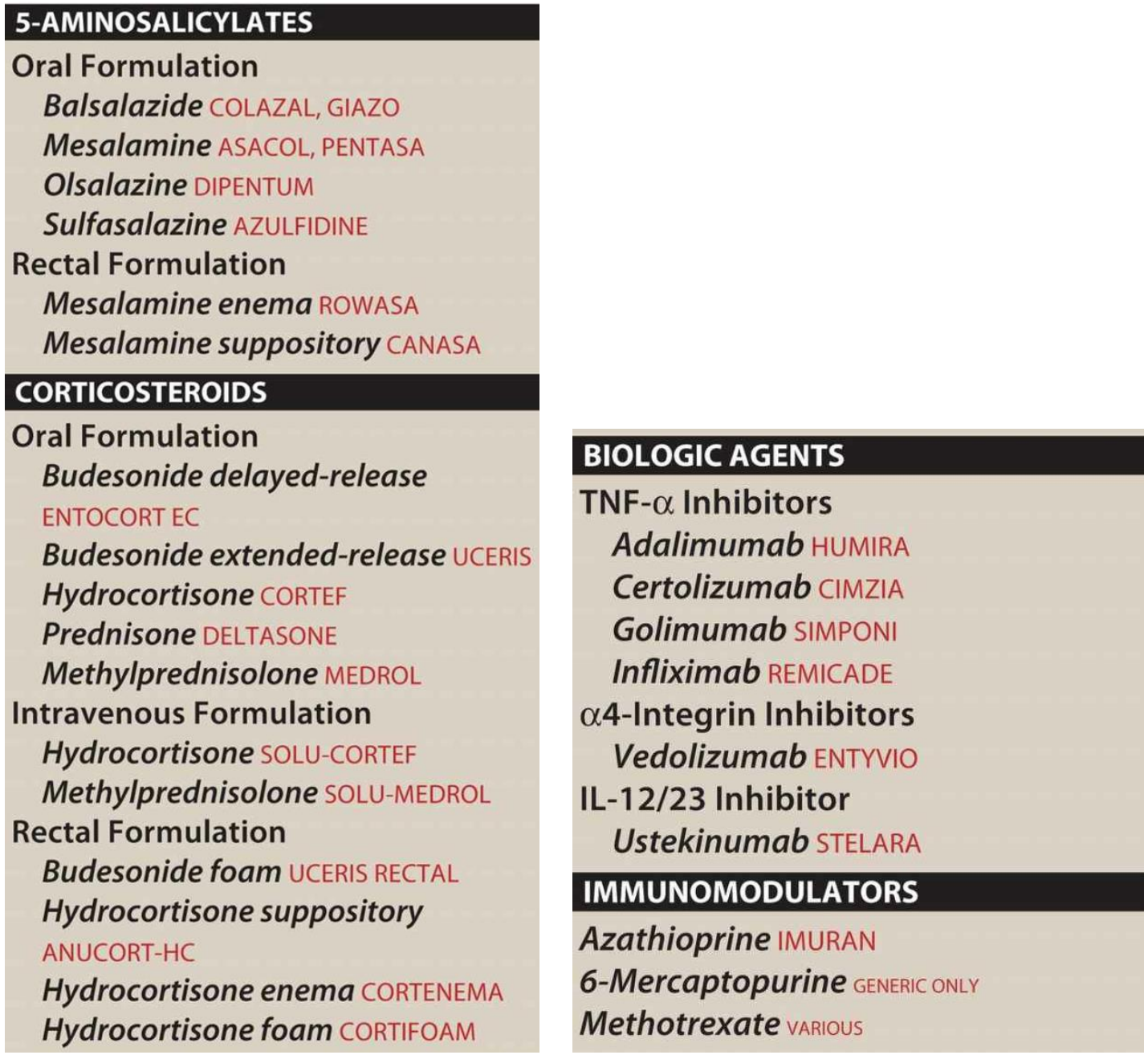

Figure 5: Agents used in the treatment of IBD.

DRUG	BRAND(S)	ROUTE	DOSING FREQUENCY	FORMULATION	SITE OF DELIVERY
Balsalazide	Colazal	PO	Three times daily	5-ASA azo bonded to inert carrier molecule; release dependent on cleavage by colonic bacteria	Colon
Mesalamine	Apriso	PO	Once daily	pH-dependent (≥ 6) delayed release with extended-release matrix core	Colon
	Asacol, Asacol HD	PO	Three times daily	pH-dependent (≥ 7) delayed release	Distal ileum, colon
	Canasa	Rectal	Once daily	Suppository	Rectum
	Lialda	PO	Once daily	pH-dependent (≥ 7) delayed-release multimatrix system	Distal ileum, colon
	Pentasa	PO	Four times daily	Ethyl cellulose membrane controlled-release micropellets	Entire small intestine, colon
	Rowasa	Rectal	Once daily	Liquid enema	Rectum, sigmoid colon
Olsalazine	Dipentum	PO	Twice daily	5-ASA azo bonded to another 5-ASA molecule; release dependent on cleavage by colonic bacteria	Colon

Figure 6: 5-Aminosalicylate formulations


Thank You!