Drugs Used in the Treatment of Gastrointestinal Diseases (II)

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Learning objectives:

Following the lesson presentation students will be able to:

1. Describe the indications, mechanism of action, side effects and contraindications of drugs stimulating gastrointestinal motility

2. Describe the indications, mechanism of action, side effects and contraindications of antiemetic agents

3. Describe the indications, mechanism of action, side effects and contraindications of antidiarrheal agents

4. Describe the indications, mechanism of action, side effects and contraindications of laxatives

DRUGS STIMULATING GASTROINTESTINAL MOTILITY

Drugs that can selectively stimulate gut motor function (**prokinetic** agents) have significant potential clinical indications including GERD, gastroparesis, postsurgical gastric emptying delay, postoperative ileus.

1. CHOLINOMIMETIC AGENTS

Cholinomimetic agonists such as **bethanechol** stimulate muscarinic M3 receptors on muscle cells and at myenteric plexus synapses. Bethanechol was used in the past for the treatment of GERD and gastroparesis. Owing to multiple cholinergic effects and the advent of less toxic agents, it is now seldom used. The acetylcholinesterase inhibitor neostigmine can enhance gastric, small intestine, and colonic emptying. Intravenous **neostigmine** is used for the treatment of hospitalized patients with acute large bowel distention. Cholinergic effects include excessive salivation, nausea, vomiting, diarrhea, and bradycardia.

2. METOCLOPRAMIDE & DOMPERIDONE

Metoclopramide and **domperidone** are dopamine D2-receptor antagonists. Within the gastrointestinal tract activation of dopamine receptors inhibits cholinergic smooth muscle stimulation; blockade of this effect is believed to be the primary prokinetic mechanism of action of these agents. These agents increase esophageal peristaltic amplitude, increase lower esophageal sphincter pressure, and enhance gastric emptying but have no effect on small intestine or colonic motility. Metoclopramide and domperidone also block dopamine D2 receptors in the chemoreceptor trigger zone of the medulla (area postrema), resulting in potent antinausea and antiemetic action.

Clinical Uses:

1. Gastroesophageal reflux disease—These agents are sometimes used in the treatment of symptomatic GERD but are not effective in patients with erosive esophagitis.

2. Impaired gastric emptying—These agents are widely used in the treatment of patients with delayed gastric emptying due to postsurgical disorders (vagotomy, antrectomy) and diabetic gastroparesis. Metoclopramide is sometimes administered in hospitalized patients to promote advancement of nasoenteric feeding tubes from the stomach into the duodenum.

3. Nonulcer dyspepsia—These agents lead to symptomatic improvement in a small number of patients with chronic dyspepsia.

4. Prevention of vomiting—Because of their potent antiemetic action, metoclopramide and domperidone are used for the prevention and treatment of emesis.

5. Postpartum lactation stimulation—Domperidone is sometimes recommended to promote postpartum lactation.

Adverse Effects: The most common adverse effects of metoclopramide involve the central nervous system. Restlessness, drowsiness, insomnia, anxiety, and agitation occur in 10–20% of patients, especially the elderly. Extrapyramidal effects (dystonias, akathisia, parkinsonian features) due to central dopamine receptor blockade occur acutely in 25% of patients given high doses and in 5% of patients receiving longterm therapy. Tardive dyskinesia, sometimes irreversible, has developed in patients treated for a prolonged period with metoclopramide. For this reason, long-term use should be avoided unless absolutely necessary, especially in the elderly. Elevated prolactin levels (caused by both metoclopramide and domperidone) can cause galactorrhea, gynecomastia, impotence, and menstrual disorders.

Domperidone is extremely well tolerated. Because it does not cross the blood-brain barrier to a significant degree, neuropsychiatric and extrapyramidal effects are rare.

3. MACROLIDES

Macrolide antibiotics such as **erythromycin** directly stimulate motilin receptors on gastrointestinal smooth muscle and promote the onset of a migrating motor complex. Intravenous erythromycin is beneficial in some patients with gastroparesis; however, tolerance rapidly develops. It may be used in patients with acute upper gastrointestinal hemorrhage to promote gastric emptying of blood before endoscopy.

ANTIEMETIC AGENTS

Nausea and vomiting may be manifestations of a wide variety of conditions, including adverse effects from medications; systemic disorders or infections; pregnancy; vestibular dysfunction; central nervous system infection or increased pressure; peritonitis; hepatobiliary disorders; adiation or chemotherapy; and gastrointestinal obstruction, dysmotility, or infections.

PATHOPHYSIOLOGY

The brainstem "vomiting center" is a loosely organized neuronal region within the lateral medullary reticular formation and coordinates the complex act of vomiting through interactions with cranial nerves VIII and X and neural networks in the nucleus tractus solitaries that control respiratory, salivatory, and vasomotor centers. High concentrations of muscarinic M1, histamine H1, neurokinin 1 (NK1), and serotonin 5-HT3 receptors have been identified in the vomiting center. There are four important sources of afferent input to the vomiting center:

1. The "chemoreceptor trigger zone" or area postrema is located at the caudal end of the fourth ventricle. This is outside the blood-brain barrier and is accessible to emetogenic stimuli in the blood or cerebrospinal fluid. The chemoreceptor trigger zone is rich in dopamine D2 receptors and opioid receptors, and possibly serotonin 5-HT3 receptors and NK1 receptors.

2. The vestibular system is important in motion sickness via cranial nerve VIII. It is rich in muscarinic M1 and histamine H1 receptors.

3. Vagal and spinal afferent nerves from the gastrointestinal tract are rich in 5-HT3 receptors. Irritation of the gastrointestinal mucosa by chemotherapy, radiation therapy, distention, or acute infectious gastroenteritis leads to release of mucosal serotonin and activation of these receptors, which stimulate vagal afferent input to the vomiting center and chemoreceptor trigger zone.

4. The central nervous system plays a role in vomiting due to psychiatric disorders, stress, and anticipatory vomiting prior to cancer chemotherapy.

Identification of the different neurotransmitters involved with emesis has allowed development of a diverse group of antiemetic agents that have affinity for various receptors. Combinations of antiemetic agents with different mechanisms of action are often used, especially in patients with vomiting due to chemotherapeutic agents.

1. SEROTONIN 5-HT3 ANTAGONISTS

Selective 5-HT3-receptor antagonists have potent antiemetic properties that are mediated in part through central 5-HT3-receptor blockade in the vomiting center and chemoreceptor trigger zone but mainly through blockade of peripheral 5-HT3 receptors on extrinsic intestinal vagal and spinal afferent nerves. The anti-emetic action of these agents is restricted to emesis attributable to vagal stimulation (eg, postoperative) and chemotherapy; other emetic stimuli such as motion sickness are poorly controlled. Three agents are available in Iran: ondansetron, granisetron and Tropisetron. All three drugs have comparable efficacy and tolerability when administered at equipotent doses. All drugs undergo extensive hepatic metabolism and are eliminated by renal and hepatic excretion. However, dose reduction is not required in geriatric patients or patients

with renal insufficiency. For patients with hepatic insufficiency, dose reduction may be required with ondansetron. 5-HT3-receptor antagonists do not inhibit dopamine or muscarinic receptors. They do not have effects on esophageal or gastric motility but may slow colonic transit.

Clinical Uses

1. Chemotherapy-induced nausea and vomiting—5-HT3-receptor antagonists are the primary agents for the prevention of acute chemotherapy-induced nausea and emesis. When used alone, these drugs have little or no efficacy for the prevention of delayed nausea and vomiting (ie, occurring > 24 hours after chemotherapy). The drugs are most effective when given as a single dose by intravenous injection 30 minutes prior to administration of chemotherapy. Although 5-HT3-receptor antagonists are effective as single agents for the prevention of chemotherapy-induced nausea and vomiting, their efficacy is enhanced by combination therapy with a corticosteroid (dexamethasone) and NK1-receptor antagonist.

2. Postoperative and postradiation nausea and vomiting—5-HT3-receptor antagonists are used to prevent or treat postoperative nausea and vomiting. Because of adverse effects and increased restrictions on the use of other antiemetic agents, 5-HT3-receptor antagonists are increasingly used for this indication. They are also effective in the prevention and treatment of nausea and vomiting in patients undergoing radiation therapy to the whole body or abdomen.

Adverse Effects: The 5-HT3-receptor antagonists are well-tolerated agents with excellent safety profiles. The most commonly reported adverse effects are headache, dizziness, and constipation. All four agents cause a small but statistically significant prolongation of the QT interval, but this is most pronounced with dolasetron.

Drug Interactions: No significant drug interactions have been reported with 5-HT3-receptor antagonists. All agents undergo some metabolism by the hepatic cytochrome P450 system but

they do not appear to affect the metabolism of other drugs. However, other drugs may reduce hepatic clearance of the 5-HT3-receptor antagonists, altering their half-life.

2. CORTICOSTEROIDS

Corticosteroids (dexamethasone, methylprednisolone) have antiemetic properties, but the basis for these effects is unknown. These agents appear to enhance the efficacy of 5-HT3-receptor antagonists for prevention of acute and delayed nausea and vomiting in patients receiving moderately to highly emetogenic chemotherapy regimens.

3. NEUROKININ RECEPTOR ANTAGONISTS

Neurokinin 1 (NK1)-receptor antagonists have antiemetic properties that are mediated through central blockade in the area postrema. Aprepitant (an oral formulation) is a highly selective NK1-receptor antagonist that crosses the blood-brain barrier and occupies brain NK1 receptors. It has no affinity for serotonin, dopamine, or corticosteroid receptors.

Clinical Uses: Aprepitant is used in combination with 5-HT3-receptor antagonists and corticosteroids for the prevention of acute and delayed nausea and vomiting from highly emetogenic chemotherapeutic regimens. Combined therapy with aprepitant, a 5-HT3-receptor antagonist, and dexamethasone prevents acute emesis in 80–90% of patients compared with less than 70% treated without aprepitant.

Adverse Effects & Drug Interactions: Aprepitant may be associated with fatigue, dizziness, and diarrhea. The drug is metabolized by CYP3A4 and may inhibit the metabolism of other drugs metabolized by the CYP3A4 pathway. Several chemotherapeutic agents are metabolized by CYP3A4, including docetaxel, paclitaxel, etoposide, irinotecan, imatinib, vinblastine, and

vincristine. Drugs that inhibit CYP3A4 metabolism may significantly increase aprepitant plasma levels (eg, ketoconazole, ciprofloxacin, clarithromycin, nefazodone, ritonavir, nelfinavir, verapamil, and quinidine). Aprepitant decreases the international normalized ratio (INR) in patients taking warfarin.

4. PHENOTHIAZINES & BUTYROPHENONES

Phenothiazines are antipsychotic agents that can be used for their potent antiemetic and sedative properties. The antiemetic properties of phenothiazines are mediated through inhibition of dopamine and muscarinic receptors. Sedative properties are due to their antihistamine activity. The agents most commonly used as antiemetics are promethazine, and thiethylperazine. Antipsychotic butyrophenones also possess antiemetic properties due to their central dopaminergic blockade. Extrapyramidal effects and hypotension may occur.

5. Metoclopramide

Metoclopramide primary mechanism of antiemetic action is believed to be dopamine-receptor blockade. For prevention and treatment of nausea and vomiting, metoclopramide may be given in the relatively high dosage of 10–20 mg orally or intravenously every 6 hours. The principal adverse effects of metoclopramide are extrapyramidal: restlessness, dystonias, and parkinsonian symptoms.

6. H1 ANTIHISTAMINES & ANTICHOLINERGIC DRUGS

As single agents, these drugs have weak antiemetic activity, although they are particularly useful for the prevention or treatment of motion sickness. Their use may be limited by dizziness, sedation, confusion, dry mouth, cycloplegia, and urinary retention. Diphenhydramine and one of its salts, dimenhydrinate, are first-generation histamine H1 antagonists that also have significant

anticholinergic properties. Because of its sedating properties, diphenhydramine is commonly used in conjunction with other antiemetics for treatment of emesis due to chemotherapy.

Meclizine is an H1 antihistaminic agent with minimal anticholinergic properties that also causes less sedation. It is used for the prevention of motion sickness and the treatment of vertigo due to labyrinth dysfunction.

Hyoscine (scopolamine), a prototypic muscarinic receptor antagonist, is one of the best agents for the prevention of motion sickness. However, it has a very high incidence of anticholinergic effects when given orally or parenterally. It is better tolerated as a transdermal patch. Superiority to dimenhydrinate has not been proved.

7. BENZODIAZEPINES

Benzodiazepines such as lorazepam or diazepam are used before the initiation of chemotherapy to reduce anticipatory vomiting or vomiting caused by anxiety.

8. CANNABINOIDS

Dronabinol is Δ9-tetrahydrocannabinol (THC), the major psychoactive chemical in marijuana.

Like crude marijuana, dronabinol is a psychoactive agent that is used medically as an appetite stimulant and as an antiemetic, but the mechanisms for these effects are not understood. Because of the availability of more effective agents, dronabinol now is uncommonly used for the prevention of chemotherapy-induced nausea and vomiting. Combination therapy with phenothiazines provides synergistic antiemetic action and appears to attenuate the adverse effects of both agents. Adverse effects include euphoria, dysphoria, sedation, hallucinations, dry mouth, and increased appetite. It has some autonomic effects that may result in tachycardia, conjunctival injection, and orthostatic hypotension. Dronabinol has no significant drug-drug interactions but may potentiate the clinical effects of other psychoactive agents.

ANTIDIARRHEAL AGENTS

Antidiarrheal agents may be used safely in patients with mild to moderate acute diarrhea. However, these agents should not be used in patients with bloody diarrhea, high fever, or systemic toxicity because of the risk of worsening the underlying condition. They should be discontinued in patients whose diarrhea is worsening despite therapy. Antidiarrheals are also used to control chronic diarrhea caused by such conditions as IBS or inflammatory bowel disease (IBD).

1. OPIOID AGONISTS

Opioids have significant constipating effects. They increase colonic phasic segmenting activity through inhibition of presynaptic cholinergic nerves in the submucosal and myenteric plexuses and lead to increased colonic transit time and fecal water absorption. They also decrease mass colonic movements and the gastrocolic reflex. Although all opioids have antidiarrheal effects, central nervous system effects and potential for addiction limit the usefulness of most. **Loperamide** is a nonprescription opioid agonist that does not cross the blood-brain barrier and has no analgesic properties or potential for addiction. Tolerance to long-term use has not been reported. It is typically administered in doses of 2 mg taken one to four times daily. **Diphenoxylate** is a prescription opioid agonist that has no analgesic properties in standard doses; however, higher doses have central nervous system effects, and prolonged use can lead to opioid dependence. Commercial preparations commonly contain small amounts of atropine to discourage overdosage (2.5 mg diphenoxylate with 0.025 mg atropine). The anticholinergic properties of atropine may contribute to the antidiarrheal action.

2. COLLOIDAL BISMUTH COMPOUNDS

Two bismuth compounds are available: **bismuth subsalicylate,** and **bismuth subcitrate.** Bismuth has direct antimicrobial effects and binds enterotoxins, accounting for its benefit in preventing and treating traveler's diarrhea.

Adverse Effects: All bismuth formulations have excellent safety profiles. Bismuth causes harmless blackening of the stool, which may be confused with gastrointestinal bleeding. Liquid formulations may cause harmless darkening of the tongue. Bismuth agents should be used for short periods only and should be avoided in patients with renal insufficiency. Prolonged usage of some bismuth compounds may rarely lead to bismuth toxicity, resulting in encephalopathy (ataxia, headaches, confusion, seizures). However, such toxicity is not reported with bismuth subsalicylate or bismuth citrate. High dosages of bismuth subsalicylate may lead to salicylate toxicity.

3. BILE SALT-BINDING RESINS

Conjugated bile salts are normally absorbed in the terminal ileum. Disease of the terminal ileum (eg, Crohn's disease) or surgical resection leads to malabsorption of bile salts, which may cause colonic secretory diarrhea. The bile salt-binding resins **cholestyramine and colestipol** may decrease diarrhea caused by excess fecal bile acids. These products come in a variety of powder and pill formulations that may be taken one to three times daily before meals. Adverse effects include bloating, flatulence, constipation, and fecal impaction. In patients with diminished circulating bile acid pools, further removal of bile acids may lead to an exacerbation of fat malabsorption. Cholestyramine and colestipol bind a number of drugs and reduce their absorption; hence, they should not be given within 2 hours of other drugs.

LAXATIVES

Intermittent constipation is best prevented with a high-fiber diet, adequate fluid intake, regular exercise, and the heeding of nature's call. Patients not responding to dietary changes or fiber supplements should undergo medical evaluation before initiating long-term laxative treatment. Laxatives may be classified by their major mechanism of action, but many work through more than one mechanism.

1. BULK-FORMING LAXATIVES

Bulk-forming laxatives are indigestible, hydrophilic colloids that absorb water, forming a bulky, emollient gel that distends the colon and promotes peristalsis. Common preparations include natural plant products **(psyllium, methylcellulose)** and synthetic fibers **(polycarbophil).** Bacterial digestion of plant fibers within the colon may lead to increased bloating and flatus.

2. STOOL SURFACTANT AGENTS (SOFTENERS)

These agents soften stool material, permitting water and lipids to penetrate. They may be administered orally or rectally. Common agents include **docusate** (oral or enema) and **glycerin suppository**. In hospitalized patients, docusate is commonly prescribed to prevent constipation and minimize straining. **Mineral oil** is clear, viscous oil that lubricates fecal material, retarding water absorption from the stool. It is used to prevent and treat fecal impaction in young children and debilitated adults. It is not palatable but may be mixed with juices. Aspiration can result in a severe lipid pneumonitis. Long-term use can impair absorption of fatsoluble vitamins (A, D, E, K).

3. OSMOTIC LAXATIVES

The colon can neither concentrate nor dilute fecal fluid: fecal water is isotonic throughout the colon. Osmotic laxatives are soluble but nonabsorbable compounds that result in increased stool liquidity due to an obligate increase in fecal fluid.

- Nonabsorbable Sugars or Salts

These agents may be used for the treatment of acute constipation or the prevention of chronic constipation. **Magnesium hydroxide (milk of magnesia)** is a commonly used osmotic laxative. It should not be used for prolonged periods in patients with renal insufficiency due to the risk of hypermagnesemia. **Sorbitol** and **lactulose** are nonabsorbable sugars that can be used to prevent or treat chronic constipation. These sugars are metabolized by colonic bacteria, producing severe flatus and cramps. High doses of osmotically active agents produce prompt bowel evacuation (purgation) within 1–3 hours. The rapid movement of water into the distal small bowel and colon leads to a high volume of liquid stool followed by bowel evacuation.

When taking these purgatives, it is very important that patients maintain adequate hydration by taking increased oral liquids to compensate for fecal fluid loss.

- Balanced Polyethylene Glycol

Lavage solutions containing **polyethylene glycol (PEG)** are commonly used for complete colonic cleansing before gastrointestinal endoscopic procedures. These balanced, isotonic solutions contain an inert, nonabsorbable, osmotically active sugar (PEG) with sodium sulfate, sodium chloride, sodium bicarbonate, and potassium chloride. The solution is designed so that no significant intravascular fluid or electrolyte shifts occur. Therefore, they are safe for all patients. For optimal bowel cleansing, 1–2 L of solution should be ingested rapidly (over 1–2 hours) on the evening before the procedure and again 4–6 hours before the procedure. For treatment or prevention of chronic constipation, smaller doses of PEG powder may be mixed with water or juices and ingested daily. In contrast to sorbitol or lactulose, PEG does not produce significant cramps or flatus.

4. STIMULANT LAXATIVES

Stimulant laxatives (cathartics) induce bowel movements through a number of poorly understood mechanisms. These include direct stimulation of the enteric nervous system and colonic electrolyte and fluid secretion. There has been concern that long-term use of cathartics could lead to dependence and destruction of the myenteric plexus, resulting in colonic atony and dilation. More recent research suggests that long-term use of these agents probably is safe in most patients. Cathartics may be required on a long-term basis, especially in patients who are neurologically impaired and in bed-bound patients in long-term care facilities.

- Anthraquinone Derivatives

Aloe, senna, and **cascara** occur naturally in plants. These laxatives are poorly absorbed and after hydrolysis in the colon, produce a bowel movement in 6–12 hours when given orally and within 2 hours when given rectally. Chronic use leads to a characteristic brown pigmentation of the colon known as "melanosis coli." There has been some concern that these agents may be carcinogenic, but epidemiologic studies do not suggest a relation to colorectal cancer.

- Bisacodyl

Bisacodyl is available in tablet and suppository formulations for the treatment of acute and chronic constipation. It also is used in conjunction with PEG solutions for colonic cleansing prior to colonoscopy. It induces a bowel movement within 6–10 hours when given orally and 30–60 minutes when taken rectally. It has minimal systemic absorption and appears to be safe for acute and long-term use.

5. CHLORIDE CHANNEL ACTIVATORS

Lubiprostone is labeled for use in chronic constipation and irritable bowel syndrome (IBS) with predominant constipation. It acts by stimulating the type 2 chloride channel (ClC-2) in the small intestine. This increases chloriderich fluid secretion into the intestine, which stimulates intestinal

motility and shortens intestinal transit time. There appears to be no loss of efficacy with long-term therapy. After discontinuation of the drug, constipation may return to its pretreatment severity. Lubiprostone has minimal systemic absorption but is designated category C for pregnancy because of increased fetal loss in guinea pigs. Lubiprostone may cause nausea in up to 30% of patients due to delayed gastric emptying.

6- OPIOID RECEPTOR ANTAGONISTS

Acute and chronic therapy with opioids may cause constipation by decreasing intestinal motility, which results in prolonged transit time and increased absorption of fecal water. Use of opioids after surgery for treatment of pain as well as endogenous opioids also may prolong the duration of postoperative ileus. These effects are mainly mediated through intestinal mu (μ)-opioid receptors. Two selective antagonists of the μ-opioid receptor are commercially available: **methylnaltrexone** bromide and **alvimopan.** Because these agents do not readily cross the blood-brain barrier, they inhibit peripheral μ-opioid receptors without impacting analgesic effects within the central nervous system. Methylnaltrexone is approved for the treatment of opioid-induced constipation in patients receiving palliative care for advanced illness who have had inadequate response to other agents.

Reference:

Katzung BG and Trevor AG. Basic and Clinical Pharmacology, McGraw-Hill, 13th edition, 2015.

MCQ: With regard to Anthraquinone, all the followings are incorrect except:

a. It is a stimulant laxative

b. It is a neurokinine-1 receptor antagonist

c. It's a parasympatholytic agent

d. It is a bulk-forming laxative