Gastrointestinal and Antiemetic Drugs

Part 2

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Drugs used to control chemotherapy-induced nausea and vomiting

- Several factors influence the incidence and severity of chemotherapy-induced nausea and vomiting (CINV), including the specific chemotherapeutic drug; the dose, route, and schedule of administration; and patient variables. Uncontrolled vomiting can produce dehydration, profound metabolic imbalances, and nutrient depletion.

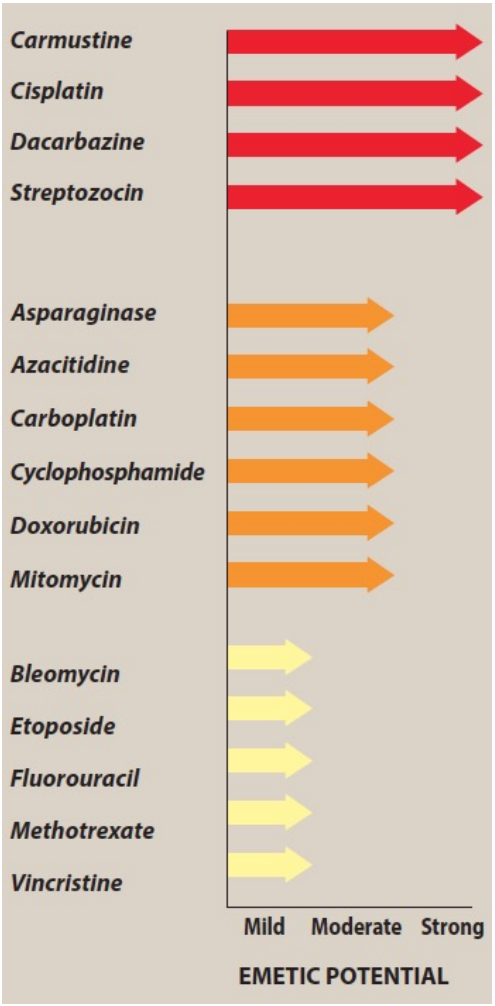
- **Mechanisms that trigger vomiting:** Two brainstem sites have key roles in the vomiting reflex pathway. **The chemoreceptor trigger zone (CTZ)** is located in the area postrema (a circumventricular structure at the caudal end of the fourth ventricle). It is outside the blood–brain barrier. Thus, it can respond directly to chemical stimuli in the blood or cerebrospinal fluid.

- 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 vomiting center also responds to afferent input from the vestibular system, the periphery (pharynx and GI tract), and higher brainstem and cortical structures. The vestibular system functions mainly in motion sickness.

Drugs used to control chemotherapy-induced nausea and 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-HT3), 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. Serotonin activates 5-HT3 receptors on vagal and splanchnic afferent fibers, which then carry sensory signals to the medulla, leading to the emetic response.



Antiemetic drugs

- Anticholinergic drugs, especially the **muscarinic receptor antagonist scopolamine** and **H1-receptor antagonists, such as dimenhydrinate, meclizine, and cyclizine**, are very useful in motion sickness but are ineffective against substances that act directly on the CTZ. The major categories of drugs used to control CINV include the following:

1. **Phenothiazines:** such as ***prochlorperazine***, act by blocking dopamine receptors. Prochlorperazine is effective against low or moderately emetogenic chemotherapeutic agents (for example, fluorouracil and doxorubicin). Although increasing the dose improves antiemetic activity, side effects are dose limiting.

2. **5-HT3 receptor blockers:** The 5-HT3 receptor antagonists include ***ondansetron, granisetron, palonosetron, and dolasetron***. These agents selectively block 5-HT3 receptors in the periphery (visceral vagal afferent fibers) and in the brain (CTZ).

Antiemetic drugs

- This class of agents is important in treating emesis linked with chemotherapy, largely 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.

- **Ondansetron and granisetron** prevent emesis in 50% to 60% of cisplatin-treated patients. These agents are also useful in the management of postoperative nausea and vomiting.

- 5-HT3 antagonists are extensively metabolized by the liver; however, only ondansetron requires dosage adjustments in hepatic insufficiency.

- Electrocardiographic changes, such as a prolonged QTc interval, can occur with dolasetron and high doses of ondansetron. For this reason, dolasetron is no longer approved for CINV prophylaxis.

Antiemetic drugs

3. Substituted benzamides: One of several substituted benzamides with antiemetic activity, ***metoclopramide*** is effective at high doses against the emetogenic cisplatin, preventing emesis in 30% to 40% of patients and reducing emesis in the majority of patients.

- Metoclopramide accomplishes this through inhibition of dopamine in the CTZ. Antidopaminergic side effects, including extrapyramidal symptoms, limit long-term high-dose use. Metoclopramide was previously used as a prokinetic drug for the treatment of GERD. However, due to the adverse effect profile and the availability of more effective drugs, such as PPIs, it should be reserved for patients with documented gastroparesis.

4. Butyrophenones: ***Droperidol and haloperidol*** act by blocking dopamine receptors. The butyrophenones are moderately effective antiemetics. Droperidol had been used most often for sedation in endoscopy and surgery, usually in combination with opioids or benzodiazepines.

- However, it may prolong the QTc interval and should be reserved for patients with inadequate response to other agents. High-dose haloperidol was found to be nearly as effective as high-dose metoclopramide in preventing cisplatin-induced emesis.

Antiemetic drugs

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

- These same properties make benzodiazepines useful in treating anticipatory vomiting. 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, however, they are used in combination with other agents. Their antiemetic mechanism is not known, but it may involve blockade of prostaglandins.

7. Substance P/neurokinin-1 receptor blocker: ***Aprepitant*** targets the neurokinin receptor in the brain and blocks the actions of the natural substance. Aprepitant is indicated only for highly or moderately emetogenic chemotherapy regimens. It is usually administered orally with dexamethasone and a 5-HT3 antagonist.

Antiemetic drugs

8. Combination regimens: Antiemetic drugs are often combined to increase antiemetic activity or decrease toxicity.

- Corticosteroids, most commonly ***dexamethasone***, increase antiemetic activity when given with high-dose ***metoclopramide***, a 5-HT3 antagonist, ***phenothiazine, butyrophenone, or a benzodiazepine***.

- Antihistamines, such as ***diphenhydramine***, are often administered in combination with high-dose ***metoclopramide*** to reduce extrapyramidal reactions or with ***corticosteroids*** to counter metoclopramide- induced diarrhea.

Antidiarrheal

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 are analogs of meperidine and have opioid-like actions on the gut. They activate presynaptic opioid receptors in the enteric nervous system to inhibit acetylcholine release and decrease peristalsis. At the usual doses, they lack analgesic effects. Because these drugs can contribute to toxic megacolon, they should not be used in young children or in patients with severe colitis.

B. **Adsorbents:** 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 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 for constipation to accelerate the movement of food through the GI tract. 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. Its active ingredient is a group of sennosides, a natural complex of anthraquinone glycosides. Taken orally, senna causes evacuation of the bowels within 8 to 10 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.

Laxatives

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**. They should be used cautiously in patients who are immobile because of their potential for causing intestinal obstruction.

C. Saline and osmotic laxatives: Saline cathartics, such as ***magnesium citrate and magnesium hydroxide***, are nonabsorbable salts (anions and cations) that hold water in the intestine by osmosis. This distends the bowel, increasing intestinal activity and producing defecation in a few hours. Electrolyte solutions containing ***polyethylene glycol (PEG)*** are used as colonic lavage solutions to prepare the gut for radiologic or endoscopic procedures.

- PEG powder for solution is available as a prescription and also as an over-the-counter laxative and has been shown to cause less cramping and gas than other laxatives.

- ***Lactulose*** is a semisynthetic disaccharide sugar that acts as an osmotic laxative. It cannot be hydrolyzed by GI enzymes. Oral doses reach the colon and are degraded 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.

Laxatives

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

- Stool softeners should not be taken concomitantly with mineral oil because of the potential for absorption of the mineral oil.

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***, currently the only agent in this class, 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.

- Lubiprostone is used in the treatment of chronic constipation, particularly because tolerance or dependency has not been associated with this drug.


Thank You!