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**Drugs acting on the GIT
Treatment of vomiting, Diarrhea and
constipation**

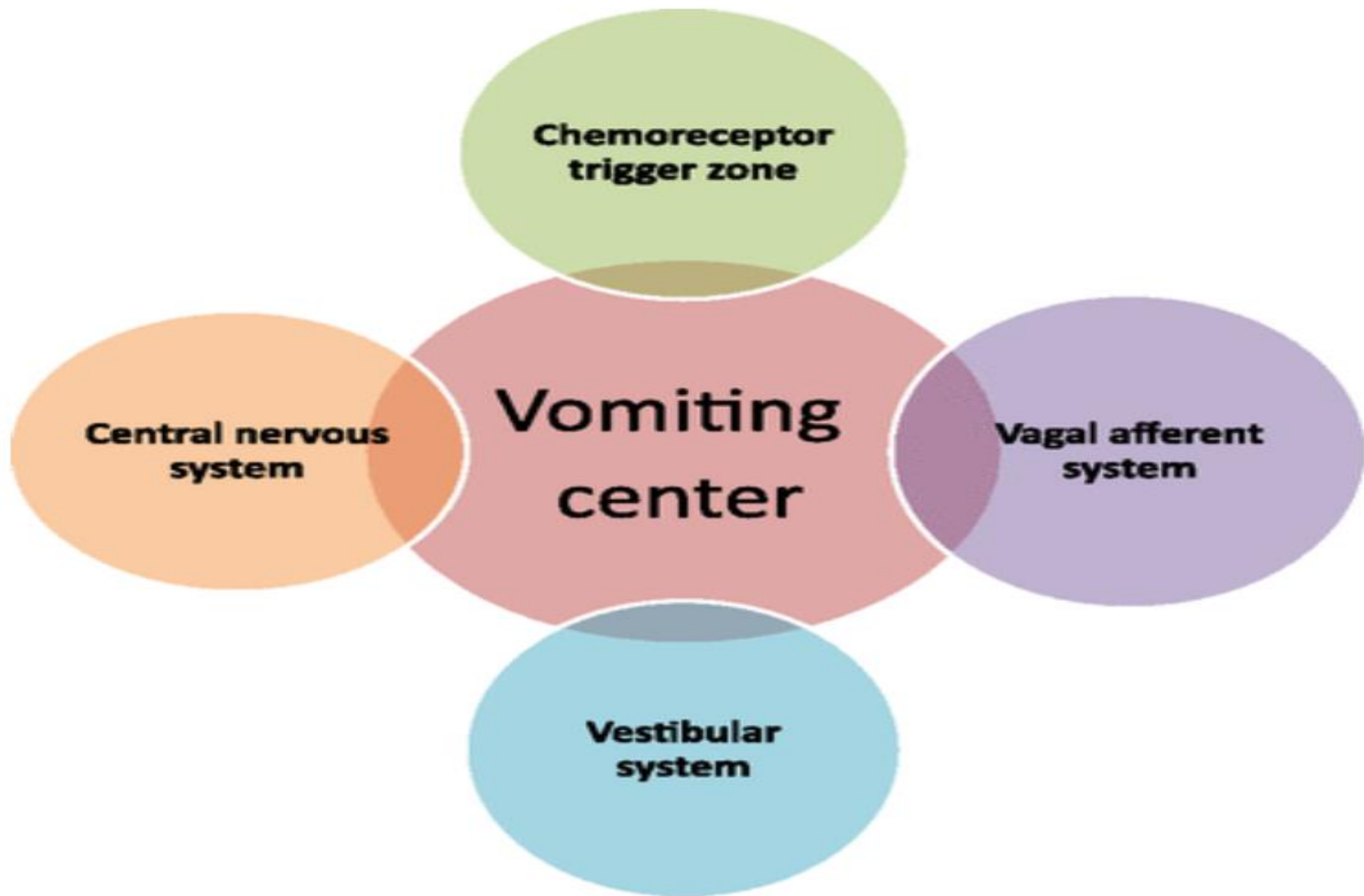
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2024**

Antiemetic drugs

➤ Nausea is a vague subjective sensation of sickness. Vomiting often follows and it is a reflex physical act of expulsion of gastric contents.

The brainstem **vomiting center** is composed of a group of neuronal areas within the medulla that coordinate emesis. It may be stimulated by four different sources of afferent input:

- 1- Afferent vagal fibers from **GIT viscera** (rich in serotonin **5-HT₃** and **muscarinic** receptors)
- 2- Fibers of the **vestibular system** (rich in histamine **H₁** and **muscarinic** receptors)
- 3- **Higher centers** in brain (amygdala area; where certain sights, smells or emotional experiences may induce vomiting)
- 4- The chemoreceptor trigger zone (**CTZ**) which is rich in **opioid**, serotonin **5-HT₃**, neurokinin 1 (**NK₁**) and dopamine **D₂** receptors.



Classifications of antiemetic drugs:

- 1- Serotonin 5-HT₃-receptor antagonists
- 2- Dopamine antagonists
- 3- Antihistaminic and anticholinergic drugs
- 4- Corticosteroids
- 5- Benzodiazepines
- 6- Cannabinoids
- 7- Neurokinin receptor antagonists.

Serotonin (5-HT₃) receptor antagonists

- Ondansetron, granisetron, and other setrons.
- Intravenous and oral preparations are available.
- Side effects include headache, dizziness, and **constipation**.
- The most dangerous side effect is **QT-prolongation in ECG** and **arrhythmias**.
- Used in **chemotherapy** or radiation induced **nausea and vomiting**.
- Used in **Postoperative** and **post-radiation** nausea and vomiting.

Anti-cholinergic drugs

- **Scopolamine** blocks M1 muscarinic receptor & prevent vestibular vomiting.
- Used as a **transdermal patch to prevent & treat motion sickness.**
- **It is used to prevent postoperative vomiting**
- **Side effects : dry mouth, vision changes, or drowsiness.**

Neurokinin receptor antagonists

- **Aprepitant** (oral) and **fosaprepitant** (IV) blocks the Neurokinin 1 (NK-1) receptor **preventing the release of substance-P**, which is an inducer of vomiting (in CTZ and vagal afferents).
- Side effects include headaches and dizziness and rarely **anaphylaxis**.
- **These drugs are effective in prevention and treatment of Chemotherapy-induced nausea and vomiting, also used in postoperative vomiting.**

Glucocorticoids

- The mechanism of action is not clearly understood. Possible mechanisms are changes in the blood-brain barrier and **decrease** the synthesis of **prostaglandin messengers**.
- Dexamethasone is used in prevention of chemotherapy and postoperative nausea and vomiting.
- Side effects are mild when used short-term and include **insomnia**, excitation, and **mood changes**. **Oral and IV formulations** are available.

Cannabinoid therapy

- ❑ **Nabilone** and **dronabinol** activate cannabinoid CB1 (inhibitory) receptors and modulate release of neurotransmitters.
- ❑ **Significant side-effects** such as euphoria, **dysphoria**, sedation, **hallucinations**, dry mouth, and increased appetite, tachycardia, **conjunctival injection**, and orthostatic **hypotension**.
- ❑ They are used in combination with other drugs (like ondansetron, aripiprazole or corticosteroids) to prevent chemotherapy induced nausea and vomiting.

Dopamine receptor antagonists

- Chlorpromazine **antagonize** the **D2 receptor** in the **vomiting center**. It is used in **severe vomiting** and intractable **high-cough**.
- Side effects: **Extrapyramidal symptoms** (Rigidity and abnormal muscle movement including dystonia and tardive dyskinesia).
- **Metoclopramide** is the most common medicine in this class and is typically used as a pro-kinetic agent to reduce nausea and vomiting.
- **Oral** and **IV** formulations are available.
- Metoclopramide can cross the BBB. It causes **hyperprolactinemia**, muscle **rigidity** and **tardive dyskinesia**.

Uses of Metoclopramide

1. **Migraine-related nausea and vomiting (with paracetamol)**
2. **Postoperative vomiting.**
3. **Vomiting of pregnancy.**
4. **Opioid related vomiting.**

Domperidone (motilium)

- Selective **peripheral** D2 receptor antagonist
- Has antiemetic effect & it increases GIT motility.
- It does not cross the BBB & has fewer adverse effects than Metoclopramide.

Antihistamines

- These drugs antagonize the histamine (H1) receptors.
- Diphenhydramine, meclizine**, promethazine are examples.
- They are widely available, generally well-tolerated, and different formulations are available.
- Sedation** is a widely reported, common side effect.
- Used in treating nausea and vomiting of pregnancy.

Benzodiazepines

- ✓ **Lorazepam** or **diazepam** are used before the initiation of **chemotherapy to reduce vomiting.**
- ✓ **Benzodiazepines are used in psychogenic and anxiety related vomiting.**

- Serotonin and neurokinin antagonists, such as ondansetron and aprepitant, are highly effective in treating chemotherapy-induced nausea and vomiting.
- Metoclopramide and antihistamines are first-line options for nausea and vomiting in pregnancy.
- Serotonin antagonists and some dopamine antagonists, such as metoclopramide, can prolong the QT interval on the ECG.
- Dopamine antagonists can cause extrapyramidal adverse effects, particularly in children.

Antidiarrheal drugs

Diarrhea is a clinical symptom characterized by increased GIT motility and increased stool frequency and liquidity of feces.

Some **drugs can cause diarrhea** during their administration e.g., angiotensin II receptors blockers, proton pump inhibitors, SSRIs, cholinesterase inhibitors, NSAIDs, and metformin.

Rehydration therapy by oral and/or intravenous fluids is also important especially if diarrhea is severe.

Specific treatment of diarrhea

- 1- Bacterial gastroenteritis: (ampicillin, **tetracycline**, **erythromycin**)
- 2- Cholera: **tetracycline**
- 3- Traveler's diarrhea: **Cotrimoxazole**, **fluroquinolones** & **bismuth subsalicylate** (modify fluid and electrolyte transport).
- 4- Typhoid fever and shigellosis: **Fluroquinolones** and others.
- 5- Parasitic or protozoal: anthelmintic or antiparasitic.

6-Somatostatine analogues (Octeriotide) in AIDS related diarrhea and patients with neuroendocrine tumors like carcinoid tumor.

7-Lactase Enzymes for treating osmotic diarrhea of lactose intolerance.

8-Clonidine: diarrhea in diabetic patients with autonomic neuropathy

N.B. Viral gastroenteritis diarrhea (rotavirus, adenovirus) is self limiting
rehydration therapy is adequate.

Nonspecific treatment (For symptomatic relief of diarrhea)

1- Anti-motility drugs

1- Antimuscarinic agents

Atropine blocks M3 receptors decreasing both GIT motility and secretion.

- Lomotil is a combination of loperamide (peripheral opioid agonist) and atropine (M3 blocker) is commonly used to stop diarrhea.

2- Peripheral opioid agonists (**diphenoxylate and loperamide**)

They activate peripheral opioid receptors, decreasing peristalsis and decreasing secretions.

These drugs should be avoided in:

1-young babies with gastroenteritis to avoid development of paralytic ileus or respiratory depression.

2- patients with **severe colitis** to avoid development of **colonic dilatation (megacolon)**.

3-infective diarrhea like cholera.

2- Adsorbents

- Activated charcoal, resins, kaolin and pectin powders** which can adsorb water and enterotoxins. Their therapeutic efficacy is minimal
- They may interfere with absorption of vitamins and other drugs.
- Following intestinal resection and cholecystectomy; bile salts may induce diarrhea. Treatment of this diarrhea is by administering **cholestyramine** which is a bile salt binding resin.

Laxatives and treatment of constipation

Constipation is a clinical symptom defined as infrequent stools (fewer than three in a week), hard stools, excessive straining or a sense of incomplete evacuation.

Laxatives: They are also named purgatives, cathartics or evacuants.

They promote defecation through acceleration of movement of food through GIT.

N.B. 4ml Castor oil → laxative effect. (laxative =mild effects, elimination of soft formed stool).

15-60 ml Castor oil → Cathartic effect. (cathartic =strong effects, elimination of liquid or semiliquid stool).

There is no prophylactic laxative but instead, Increasing intake of fluid, high-fiber foods, exercise are much preferred.

1-Irritants (Stimulants) laxatives

Example: **bisacodyl, senna** and **castor oil**.

Mechanism: They stimulate the **colonic nerves** & stimulate secretions in the lumen of the colon (**prostaglandin-mediated**) leading to **colonic distension** and reflex **colonic contraction**.

The laxative effect appears within 8-12 hours, therefore, oral dosing at bedtime is recommended.

Adverse effects:

1- **Abdominal cramps** and **nausea** are common side effects.

2- On chronic use, electrolyte disturbance and atonic nonfunctioning colon may develop.

3- Irritant laxative may cause reflex uterine contraction; they are **contraindicated during menstruation, pregnancy and lactation**.

4- Habituation (dependence) to their laxative effects in elderly might occur.

2- Stool softeners (emollients) laxatives

Docusate sodium:

- It **reduce the surface tension of stool material** allowing penetration of intestinal fluid into the fecal mass softening it for easy passage.
- It has also a weak stimulant property.
- It should be avoided with mineral oil to avoid increased absorption of the later.

3- Lubricant laxatives

Paraffin oil and other mineral oils

- They facilitate the passage of hard stool by **coating and softening** it.
- These drugs **inhibit water re-absorption by colon**.
- Frequently Used in children.
- Regular use of mineral oil may interfere with fat soluble vitamin absorption.
- Should not be taken more than 2 weeks by debilitated patients to avoid **(oil aspiration pneumonia)**.

4- Bulking forming laxatives

1-Natural sources like Psyllium & bran

2- Synthetic like methylcellulose.

- Mechanism of action: In the GIT, the fibers absorb water and swell forming a bulky mass (viscous liquid) that cause colonic distension and increased peristaltic activity.
- They should be given with excess water or fluids to avoid dehydration or stool impaction with intestinal obstruction.
- The major side effect is Bloating.

5- Opioid receptor antagonists

In patients who receive palliative treatment with opioids to control severe pain in advanced illness like cancer, methylnaltrexone as a peripheral μ -opioid receptor antagonist can be used to relieve opioid-induced constipation.

methylnaltrexone blocks opioid receptors in GIT without affecting central analgesia

6-Osmotic laxatives

Examples:

1- Saline laxatives like polyethylene glycol, Glycerin, **magnesium salts** (e.g., magnesium hydroxide & magnesium citrate)

2-Non-digestible non-absorbable carbohydrates like **lactulose**.

Mechanism of action: These are non-absorbable osmotic agents that **increase secretion of water into the intestinal lumen by osmosis.**

Therefore, the water and fluid content of intestine increases leading to colonic distension and softening of stool promoting defecation.

These drugs are suitable for emptying the bowel before surgery, radiological or colonoscopy procedures.

lactulose

- Lactulose is a non-absorbable disaccharide (fructose and galactose) which resists hydrolysis by disaccharidase enzyme.
- The colonic bacteria metabolize lactulose into lactic acid, acetic acid & formic acid making the colonic medium of low pH (i.e. **acidic**).
- Acidification of luminal content in the colon **stimulates colonic motility and increases osmotic pressure** with consequent fluid accumulation that create soft stool causing defecation.
- Lactulose is of therapeutic significance when given in patients with hepatic encephalopathy as the lowering of colonic pH (acidification) by the drug **discourages the growth of ammonia producing organisms in the colon and encourage nitrogen excretion as NH₄**.
- This reduces ammonia absorption from the intestine to be detoxified by the diseased liver.
- Side effects of lactulose include **Diarrhea, flatulence**, abdominal **cramps** and **discomforts**. **Dehydration** may occur. It may be **abused** by patients suffering from **bulimia nervosa** (bulimic patients).

Clinical uses of laxatives:

1. To relieve constipation.
2. To prevent straining and piles.
3. To empty the bowel in preparation for bowel surgery or diagnostic procedures.
4. To accelerate elimination of potentially toxic substances from the GIT.
5. To accelerate excretion of parasite after anti-helminthic drugs.



Thank you