Antiemetic drugs

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contents

- Vomiting definition.
- Sources of the afferent input to the vomiting center.
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Vomiting (known medically as emesis) is the forceful expulsion of the contents of the stomach through the mouth and sometimes the nose. The feeling that one is about to vomit is called nausea, which usually precedes, but does not always lead to, vomiting.
There are five sources of the afferent input to the vomiting center:

- The chemoreceptor trigger zone has numerous **dopamine D_2 receptors**, **serotonin 5-HT_3 receptors**, **opioid receptors**, **acetylcholine receptors**.

- **Cranial nerve X** which is activated when the **pharynx** is irritated, leading to a gag reflex.
The vestibular system which sends information to the brain via cranial nerve VIII (vestibulocochlear nerve). It plays a major role in motion sickness and is rich in muscarinic receptors and histamine H1 receptors.

Vagal and enteric nervous system inputs that transmit information regarding the state of the gastrointestinal system. Irritation of the GI mucosa by chemotherapy, radiation, distention, or acute infectious gastroenteritis activates the 5-HT3 receptors of these inputs.

The CNS mediates vomiting arising from psychiatric disorders and stress from higher brain centers.
Pathophysiology of Emesis

Cancer chemotherapy
Opioids

Chemoreceptor
Trigger Zone (CTZ)
(Outside BBB)
Dopamine D₂
5 HT₃, Opioid Receptors

Vomiting Centre
(medulla)
Muscarinic, 5 HT₃ & Histaminic H₁

Cerebral cortex
Smell
Sight
Thought
Anticipatory emesis

Motion sickness

Pharynx & GIT
5 HT₃ receptors

Chemo & radio therapy
Gastroenteritis

Vestibular nuclei
Muscarinic Histaminic H₁
Physiology of Post Operative Nausea and Vomiting (PONV)

<table>
<thead>
<tr>
<th>$H_1R$</th>
<th>Histamine receptors</th>
<th>$5HT_3R$</th>
<th>Serotonin (5-hydroxytryptamine) receptors</th>
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<tbody>
<tr>
<td>$D_2R$</td>
<td>Dopamine receptors</td>
<td>$ACh$</td>
<td>Acetylcholine</td>
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</table>

- **VOMITING CENTRE**
  - $H_1R$
  - Labyrinths
  - $ACh$
  - Vestibular and cerebellar nuclei
  - $ACh$

- **Chemoreceptor Trigger Zone**
  - $5HT_3R$
  - $D_2R$

- **Emetic drugs**
- **Dopamine**
- **Gut**
  - $5HT_3R$
  - Peripheral pain receptors
  - Chemoreceptors and baroreceptors
Causes

Causes in the digestive tract

1. Gastritis (inflammation of the gastric wall, usually by viruses).
2. Gastroenteritis.
3. Bowel obstruction.
4. Overeating.
5. Food allergies.
6. Food poisoning.

Pregnancy
Causes in the sensory system

- **Movement:** motion sickness

Causes in the brain

- Cerebral hemorrhage
- Migraine
- Brain tumors

Metabolic disturbances (these may irritate the stomach and the brain that coordinate vomiting)

- Hypercalcemia, Hypoglycemia, Hyperglycemia
- Uremia
- Adrenal insufficiency
Drug reaction

1. alcohol
2. opioids
3. selective serotonin reuptake inhibitors
4. many chemotherapy drugs
5. Digoxin
6. Antiparkinsonian drugs (dopamenergic drugs)
Which group of drugs can be used as antiemetics?

- Serotonin 5 HT$_3$ Antagonists
- Dopamine D$_2$ Antagonist
- Anticholinergics
- H$_1$ Antihistaminics
- Cannabinoids
- Steroids
- Others, as anxiolytic; neurokinin-1 blocker
Metoclopramide (Plasil)

- Metoclopramide acts *centrally* by blocking dopamine D2 receptors in the CTZ, and *peripherally* by enhancing the action of acetylcholine at muscarinic nerve endings in the gut. It relaxes the pyloric antrum and increases peristalsis and emptying of the upper gut. If an opioid has been given, metoclopramide may fail to overcome the opioid-induced inhibition of gastric emptying and thus the risk of vomiting and inhaling gastric contents remains. The action of metoclopramide is terminated by metabolism in the liver (t1/2 4 h).
**Uses:** Metoclopramide is used for nausea and vomiting associated with gastrointestinal disorders, with cytotoxic drugs and radiotherapy. It is also an effective antiemetic in migraine.

**Adverse reactions** are characteristic of dopamine receptor antagonists and include extrapyramidal dystonia which occurs more commonly in children and young adults, and in those who are concurrently receiving other dopamine receptor antagonists, e.g. phenothiazine drugs. Metoclopramide stimulates prolactin release and may cause gynaecomastia and lactation. Restlessness and diarrhoea may also occur.
METOCLOPRAMIDE

BRAIN

Anti-vomiting

Strengthens muscle tone

Esophagus

Relaxes passage

Metoclopramide

Stimulates contractions

Small intestine

STOMACH
Domperidone

Domperidone is a selective dopamine D₂ receptor antagonist; unlike metoclopramide it does not possess an acetylcholine-like effect. The t₁/₂ is 7 h. Domperidone does not readily penetrate the blood-brain barrier; this does not limit its therapeutic efficacy, for the CTZ is functionally out with the barrier, but there is less risk of adverse effects in the central nervous system.

Uses: Domperidone is used for nausea or vomiting associated with gastrointestinal disorders and with cytotoxic and other drug treatment. It may cause gynaecomastia.
Which is a better tolerated antiemetic – Metoclopramide or Domperidone?

Both have antiemetic effects.

But as metoclopramide crosses BBB it has adverse effects like extrapyramidal side effects.

Domperidone is well tolerated.
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. The agents most commonly used as antiemetic are prochlorperazine & promethazine.

Antipsychotic butyrophenones also possess antiemetic properties due to their central dopaminergic blockade. The main agent used is haloperidol & Droperidol. Droperidol used for postop. nausea & vomiting, but cause ECG QT prolongation.
Selective 5-HT3-receptor antagonists have potent antiemetic properties that are mediated mainly through central 5-HT3-receptor or blockade in the vomiting center and chemoreceptor trigger zone and blockade of peripheral 5-HT3 receptors on extrinsic intestinal vagal nerve. The antiemetic action of these agents is restricted to emesis attributable to vagal stimulation (e.g., postoperative) and chemotherapy; agents are available: ondansetron, granisetron, dolasetron, and palonosetron, Palonoseyron (T1/2: 40Hr).
- High first pass metabolism
- Excreted by liver & kidney
- No dose reduction in renal insufficiency but needed in hepatic insufficiency

- Given once or twice daily – orally or intravenously

**Uses**

A. chemotherapy-induced nausea and vomiting:

5-HT3-receptor antagonists are the primary agents for the prevention of acute chemotherapy-induced nausea and emesis.
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).
B. postoperative and post-radiation nausea and vomiting:

- Side effects: constipation, headache and a feeling of flushing in the head and epigastrium & cardiac arrhythmias may occur (All four drugs cause prolongation of QT interval, but more pronounced with dolasetron).
ANT1HISTAMINES & ANTICHOLINERGICS

- As a single agents, these drugs have weak anti-emetic 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, and urinary retention. Diphenhydramine are first generation histamine H₁ antagonists that 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.
Most effective drugs for motion sickness

Drugs available

- Meclizine
- Cyclizine
- Dimenhydrinate
- Diphenhydramine
- Promethazine – Used in pregnancy, used by NASA for space motion sickness
Scopolamine (hyoscine) – used as transdermal patch for motion sickness

**BENZODIAZEPINES**

Benzodiazepines such as lorazepam, diazepam and midazolam are used prior to the initiation of chemotherapy to reduce vomiting caused by anxiety. Combination with 5-HT3 antagonists is very effective in post operative vomiting.
CORTICOSTEROIDS

- Corticosteroids (dexamethasone, methylprednisolone) have antiemetic properties. 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. Although a number of corticosteroids have been used, dexamethasone 8-20 mg intravenously before chemotherapy, followed by 8 mg/d orally for 2-4 days, is commonly administered.
cannabinoid

- Nabilone is a synthetic cannabinoid and has properties similar to tetrahydrocannabinol (the active constituent of marijuana) which has an antiemetic action. It is used to relieve nausea or vomiting caused by cytotoxic drugs.

- Adverse effects include: dry mouth, decreased appetite, dizziness, euphoria, postural hypotension, confusion and psychosis. These may be reduced if prochlorperazine is given concomitantly.
neurokinin receptor antagonist:

- A protein called substance P is involved in transmitting nerve messages to the vomiting centre. Substance P acts on neurokinin-1 receptors that are found in the vomiting centre in the brain.

- Chemotherapy causes substance P to activate these neurokinin-1 receptors, resulting in feelings of sickness.

- aprepitant, which is a type of medicine called a neurokinin receptor antagonist. It is used to prevent nausea and vomiting that can be caused by chemotherapy treatment for cancer.
Aprepitant works by blocking the neurokinin-1 receptors in the brain. This stops substance P from acting on them and so prevents nausea and vomiting.

Aprepitant is used to prevent acute and delayed sickness that can be caused by chemotherapy, in particular by a medicine called cisplatin. It is given in combination with a steroid, eg dexamethasone, and a 5HT3 antagonist, e.g. ondansetron.

Adverse effects:

- Inhibiting P450
- Decrease prothrombin time in Warfarin treated patients
Now answer this question

- A physician prescribed Tab.Ondansetron for prophylaxis of motion sickness. Even though ondansetron is a potent antiemetic it didn’t produce any effect in this patient. Can you explain why?
Explanation:

Vestibular nuclei has only muscarinic and H₁ histaminic receptors.