

Gastrointestinal Pharmacology: Antiemetics

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Antiemetics are used to prevent or stop vomiting; they act on the esophagus, stomach, intestines and even on the central nervous system where the vomiting center is located. In this article, we will cover in detail the various antiemetics, their mechanism of action, adverse effects/toxicity, contraindications, drug interactions and drugs of choice. Other important pharmacological and therapeutic aspects of individual drugs will also be noted.



Definition of Antiemetics

Antiemetics is a group of drugs that suppress or prevent vomiting. The **chemoreceptor trigger zone (CTZ)**, the vestibular system, vagal and spinal afferents and other areas in the central nervous system relay to the **nucleus tractussolitarius (NTS, the vomiting center)**. As the CTZ (in area postrema) is unprotected by the blood brain barrier, it is exposed to drugs in the bloodstream, hormones, toxins and other substances that may stimulate emesis.

Pathophysiology of Emesis

Radiation, cytotoxic drugs and other gastrointestinal irritants cause the release of **5-HT** from **enterochromaffin cells**, which in turn acts on **5-HT₃ receptors** present on the extrinsic primary **afferent neurons** of the enteric nervous system. These afferent

neurons have connections with **vagal and spinal visceral afferents**, which send impulses to the NTS and CTZ. As 5-HT is released in large quantities, it may spill over into the circulation and reach the CTZ. It may be released from platelets as well due to the effect of inflammatory mediators. However, 5-HT is not the only mediator involved in such signals; many peptides and other messengers are also involved.

When the body is rotated or equilibrium is disturbed—or as a result of ototoxic drugs—the **vestibular apparatus** generates impulses. These impulses reach the vomiting center in the **medulla oblongata** (mainly via the **cerebellum**) and utilize muscarinic as well as H1 receptors. Unpleasant sensory stimuli such as a ghastly vision, bad odor, severe pain as well as fear, recalling of a dreaded event or anticipation of an emetic stimulus (such as a repeat dose of Cisplatin) cause nausea and vomiting through higher centers.

Nausea is usually accompanied by reduced gastric tone and peristalsis. In the vomiting response, the fundus and body of the stomach, the **esophageal sphincter** and the **esophagus** relax, while the duodenum and pylorus contract in a retrograde manner. **Rhythmic contractions** of the **diaphragm** and **abdominal muscles** then cause compression of the **stomach**, evacuating its contents via the **mouth**. Conditions that inhibit gastric emptying predispose to vomiting.

Classification of Antiemetics

Antiemetics are classified on the basis of their target receptors. The **CTZ** and **NTS** express many receptors including histamine (H1), serotonin (5-HT3), cholinergic (muscarinic), dopamine (D2), opioid and probably NK1.

	Category	Drugs
1	Serotonin (5-HT3) antagonists	Ondansetron , Granisetron, Dolasetron, Palonosetron, Tropisetron
2	Corticosteroids	Dexamethasone , Methylprednisolone
3	Neurokinin receptor antagonists	Aprepitant , Fosaprepitant
4	Phenothiazines and Butyrophenones	Prochlorperazine, Promethazine , Thiethylperazine, Droperidol, Doxylamine
5	Substituted Benzamides/Prokinetics	Metoclopramide , Trimethobenzamide Domperidone
6	H1 antihistamines	Diphenhydramine, Dimenhydrinate, Meclizine, Hyoscine (Scopolamine)
7	Benzodiazepines	Diazepam, Lorazepam
8	Cannabinoids	Dronabinol, Nabilone

- setrons are 5-HT3 antagonists
- azepams are Benzodiazepines

Individual drugs

Ondansetron: This **selective 5-HT3 antagonist** acts mainly by affecting the **peripheral 5-HT3 receptors** on the spinal and vagal afferents. Therefore, vomiting related to **vagal stimulation** (like **postoperative vomiting**) and chemotherapy-associated emesis are effectively controlled with this drug. **Motion sickness-related** vomiting is poorly controlled.

Ondansetron, Granisetron, and Dolasetron have a serum half-life of 4-9 hours. They are administered once daily orally or intravenously. They are usually administered 30 minutes prior to **chemotherapy**.

Granisetron is 10-15 times more potent than Ondansetron.

Palonosetron has a greater affinity to **5-HT₃ receptors** and its serum half-life is 40 hours.

All of the above drugs undergo **hepatic metabolism** (dose reduction is not needed in renal disease).

These drugs are generally well-tolerated and safe. They can **prolong the QT interval** (most prolongation is accomplished with Dolasetron).

Dexamethasone: This corticosteroid **potentiates the effect of 5-HT₃ antagonists**, especially in cases of chemotherapy. Side effects of steroids include **weight gain, osteoporosis**, increased hair growth, etc., and should be used only in highly **emetogenic chemotherapy**.

Aprepitant: This **Neurokinin receptor (NK1) antagonist** acts on the area postrema (central blockade). It is taken **orally** and has a half-life of 12 hours.

Fosaprepitant is administered **intravenously** and gets converted to Aprepitant within 30 minutes of infusion. Aprepitant undergoes hepatic metabolism (**CYP3A4**).

These drugs are used in combination with a **5-HT₃ antagonist** and a corticosteroid to prevent delayed emesis in chemotherapy patients. Side effects include fatigue, **diarrhea**, and dizziness. Drugs that **inhibit CYP3A4** (eg., Ketoconazole, Ciprofloxacin, Clarithromycin) may lead to increased plasma levels of Aprepitant. It can also **decrease the INR** in individuals on Warfarin.

Promethazine and other phenothiazines have antiemetic and sedative actions in addition to being **antipsychotics**. Promethazine has a duration of action of 4-6 hours. Adverse effects include dryness of mouth and sedation. Intravenous administration can cause severe **tissue injury**, burning or **thrombophlebitis**, leading to even **gangrene** and the need for amputation. The preferred mode of administration is deep intramuscular. It is avoided in children less than 2 years old due to the risk of **respiratory depression**. It is metabolized in the liver (CYP2D6) and has a half-life of 10 hours (i.m.), 9-16 hours (i.v.), and 16-19 hours (oral).

Droperidol, an antipsychotic butyrophenone, exhibits antiemetic properties secondary to central dopaminergic blockade. The onset of action is within 3-10 minutes of intake. Usually, its action lasts for 2-4 hours, though sometimes it reaches up to 12 hours. Side effects include extrapyramidal symptoms and hypotension. It may cause QT prolongation leading to **torsades de pointes**.

Doxylamine is an H₁ antihistaminic that has a pronounced anticholinergic activity. It is specifically promoted in India in combination with Pyridoxine for **pregnancy-related emesis**. However, it is not recommended for this use in the USA or the UK.

Metoclopramide is thought to prevent emesis by **dopamine receptor blockade**. It enhances **gastric peristalsis** and causes relaxation of the pylorus and the proximal duodenum. Consequently, gastric emptying is sped up. Moreover, it increases the lower esophageal sphincter tone, preventing **gastroesophageal reflux**. Its antiemetic action is brought about by **antidopaminergic (D₂)** action on the CTZ. Adverse effects include sedation, dizziness, **galactorrhea, gynecomastia** and **extrapyramidal features** like dystonia, **parkinsonism**, and restlessness. It can block the therapeutic action of levodopa due to DA receptor blockade in the basal ganglia.

Domperidone is a **D2 antagonist**, related chemically to Haloperidol, but related pharmacologically to Metoclopramide. However, it has a lower antiemetic and **prokinetic effect** when compared to Metoclopramide. Domperidone crosses the blood-brain barrier poorly and hence, extrapyramidal side effects are rare, but **hyperprolactinaemia** may occur. It acts on the CTZ which is not protected by the blood-brain barrier. It has been administered with Levodopa and Bromocriptine as it counteracts their dose-limiting emetic action in parkinsonism, while the therapeutic effect remains unchanged. Domperidone is absorbed orally, but due to considerable first-pass metabolism, bioavailability is only 15%. The metabolites are released via urine. Its plasma half-life is around 7.5 hours. Side effects are less compared to Metoclopramide. However, **cardiac arrhythmias** have been reported with rapid intravenous administration.

Diphenhydramine is a first-generation H1 antihistaminic agent which has a good sedative effect. It is indicated for **motion sickness**. Its onset of action is within 15-30 minutes, and its duration reaches up to 10-12 hours. It undergoes first-pass metabolism in the liver, and the metabolites are excreted mainly via urine. Side effects include **anticholinergic effects** like dry mouth, cycloplegia, urinary retention, and confusion.

Meclizine is also an H1 antihistaminic, which has a lot less anticholinergic effects. Other than its use for motion sickness, it may also be used for the treatment of **vertigo** due to **labyrinthitis**. Its onset of action is within 30-60 minutes and lasts for 12-24 hours. It is metabolized in the liver (**CYP2D6**).

Hyoscine (Scopolamine) is a muscarinic receptor antagonist which is one of the **most preferred agents for motion sickness**. As the anticholinergic manifestations are high when administered orally or parenterally, it is usually used as a **transdermal patch**. The transdermal patch contains 1.5 mg of Hyoscine which can be placed behind the pinna and delivers the drug over a span of three days. This patch should be applied four hours before the planned travel. Hyoscine is metabolized by the liver and excreted in the urine. It has a half-life of 9.5 hours.

Lorazepam and Diazepam are used prior to chemotherapy to decrease anticipatory or anxiety-related vomiting. They increase the **frequency of opening** of GABA_A: BZD receptor-Cl⁻ Channels. Its onset of action is within 1-3 minutes and lasts for up to 8 hours. It undergoes **glucuronic acid conjugation** in the liver, and the inactive metabolites are excreted via urine.

Dronabinol is, in fact, Δ^9 -**tetrahydrocannabinol (THC)**, the main psychoactive constituent in marijuana. It undergoes significant first-pass metabolism in the liver, and its metabolites are excreted gradually over days to weeks. Its major use is to prevent chemotherapy-related emesis. **Tachycardia**, **conjunctival congestion**, and **orthostatic hypotension** are the autonomic side effects associated.

Nabilone is a related **THC analog** approved for clinical use in the USA. It acts on cannabinoid receptors in the central nervous system. It should be avoided in emotionally disturbed patients and those with **concomitant alcoholism** or use of psychotropic drugs. It can affect driving and the ability to perform hazardous tasks. The elimination half-life for the parent compound is two hours and that for the metabolites is 35 hours. A good part is excreted via bile after undergoing metabolism by direct enzymatic oxidation.

Review Questions

The correct answers can be found below the references.

1. An elderly lady scheduled for chemotherapy was found to have a prolonged QT interval. Which of the following drugs should be avoided?

- A. Dolasetron
- B. Aprepitant
- C. Dexamethasone
- D. Fosaprepitant
- E. Lorazepam

2. Which of the following is most useful for the treatment and prevention of motion sickness?

- A. Granisetron
- B. Droperidol
- C. Aprepitant
- D. Ondansetron
- E. Hyoscine

3. A 70-year-old man is scheduled for chemotherapy. He had undergone cardiac surgery in the past and is on Warfarin. Which of the following drugs should be used with caution?

- A. Ondansetron
- B. Lorazepam
- C. Aprepitant
- D. Meclizine
- E. All of the above

References

Katzung BG, Masters S, Trevor A. Basic and Clinical Pharmacology 12/E. McGraw Hill Professional; 2012. p.1097-1100

Tripathi KD. "Chapter 47: Drugs for Emesis, Reflux and Digestive Disorders" in Essentials of Medical Pharmacology. JP Medical Ltd; 2013.

Correct answers: 1A; 2E; 3C

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