Emesis and antiemetic drugs

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• In emesis the stomach empties in a retrograde manner. The pyloric sphincter is closed while the cardia and esophagus relax to allow the gastric contents to be propelled orally by a forceful, synchronous contraction of abdominal wall muscles and diaphragm.

• Closure of the glottis and elevation of the soft palate prevent entry of vomitus into the trachea and nasopharynx.
• As a rule, there is prodromal salivation or yawning. Coordination between these different stages depends on the medullary center for emesis, which can be activated by diverse stimuli.

• These are conveyed via the: vestibular apparatus, visual, olfactory, and gustatory inputs, as well as viscerosensory afferents from the upper alimentary tract.

• Furthermore, psychic experiences may also activate the emetic center.

• The mechanisms underlying motion sickness (kinetosis, sea sickness) and vomiting during pregnancy are still unclear.
• Polar substances cannot reach the emetic center itself because it is protected by the blood-brain barrier. However, they can indirectly excite the center by activating chemoreceptors in the area postrema or receptors on peripheral vagal nerve endings.
A. Emetic stimuli and antiemetic drugs

Chemoreceptor trigger zone

- It is also called **area postrema**.
- It is located at the caudal end of the fourth ventricle.
- It is outside the blood-brain barrier, but accessible to emetogenic stimuli in the blood and cerebrospinal fluid.
- It is rich in dopamine D$_2$ receptors and opioid receptors, and possibly serotonin 5-HT$_3$ receptors and NK$_1$ receptors.
Antiemetic therapy.

• Vomiting can be a useful reaction enabling the body to eliminate an orally ingested poison.

• Antiemetic drugs are used to prevent:
  • kinetosis,
  • pregnancy vomiting,
  • cytotoxic drug-induced
  • postoperative vomiting,
  • as well as vomiting due to radiation therapy
Motion sickness.

- Effective prophylaxis can be achieved with the:
  - parasympatholytic scopolamine
  - H1 antihistamines of the diphenylmethane type (e.g., diphenhydramine, meclizine).
- Antiemetic activity is not a property shared by all parasympatholytics or antihistamines.
- The efficacy of the drugs mentioned depends on the actual situation of the individual:
  - (gastric filling,
  - ethanol consumption),
  - environmental conditions (e.g., the behavior of fellow travellers),
  - and the type of motion experienced.
Motion sickness.

• The drugs should be taken 30 min before the start of travel and repeated every 4 to 6 h.
• Scopolamine applied transdermally through an adhesive patch can provide effective protection for up to 3 d.
Pregnancy vomiting

- **Pregnancy vomiting** is prone to occur in the first trimester; thus pharmacotherapy would coincide with the period of maximal fetal vulnerability to chemical injury.

- Accordingly, antiemetics (antihistamines, or neuroleptics if required) should be used only when continuous vomiting threatens to disturb electrolyte and water balance to a degree that places the fetus at risk.
Drug-induced vomiting

• To prevent vomiting during anticancer chemotherapy (especially with cisplatin), effective use can be made of 5-HT3-receptor antagonists (e.g., ondansetron, granisetron, and tropisetron), alone or in combination with glucocorticoids (methylprednisolone, dexamethasone).

• **Dexamethasone 8-20 mg iv. before chemotherapy, followed by 8 mg/d orally for 2-4 days, is commonly administered.**
Central Nervous System.

- Serotonergic neurons play a part in various brain functions, as evidenced by the effects of drugs likely to interfere with serotonin.
- *Fluoxetine* is an antidepressant that, by blocking re-uptake, inhibits inactivation of released serotonin. Its activity spectrum includes:
  - significant psychomotor stimulation
  - depression of appetite,
  - and anxiolysis.
- *Buspirone* also has anxiolytic properties thought to be mediated by central presynaptic 5-HT1A receptors.
- *Ondansetron*, an antagonist at the 5-HT3 receptor, possesses striking effectiveness against cytotoxic drug-induced emesis, evident both at the start of and during cytostatic therapy.
- *Tropisetron* and *granisetron* produce analogous effects.
• Serotonin receptors and actions
Anticipatory nausea

• **Anticipatory nausea** and vomiting, resulting from inadequately controlled nausea and emesis in patients undergoing cytotoxic chemotherapy, can be attenuated by a benzodiazepine such as *lorazepam*.

• Dopamine agonist-induced nausea in parkinsonian patients can be counteracted with D2-receptor antagonists that penetrate poorly into the CNS (e.g., *domperidone, sulpiride*).
• **Metoclopramide** is effective in nausea and vomiting of gastrointestinal origin (5-HT4-receptor agonism) and at high dosage also in chemotherapy- and radiation- induced sickness (low potency antagonism at 5-HT3- and D2-receptors).

• Phenothiazines (e.g., levomepromazine, trimeprazine, perphenazine) may suppress nausea/emesis that follows certain types of surgery or is due to opioid analgesics, gastrointestinal irritation, uremia, and diseases accompanied by elevated intracranial pressure.

• The synthetic cannabinoids **dronabinol** and **nabilone** have antinauseant/antiemetic effects that may benefit AIDS and cancer patients.