DECONTAMINATION AGENTS and ANTIEMETICS
*** This material probably won’t be covered in lecture, but you are responsible for it ***

REFERENCES: Katzung (9th ed.) pp. 1051-1053
Goodman and Gilman (11th ed.) pp. 1000-1005

CRITICAL FACTS

1. Emetics can act either centrally (on the CTZ or the vomiting center) or peripherally on the GI tract or both. Therefore, in determining the mechanism of action of emetic and antiemetic drugs, it is important to consider both the location of the receptors in a particular pathway, and whether the receptors are inside or outside the blood-brain barrier.

2. Use of IPECAC to induce vomiting is no longer recommended. Problems can arise if it is administered with activated charcoal or if the suspected poison is corrosive, a petroleum distillate or a rapidly-acting convulsant.

3. 5HT₃ antagonists (DOLASETRON, GRANISETRON, ONDANSETRON) are the only agents that are truly effective in ameliorating cancer chemotherapy induced emesis (esp. caused by cisplatin). SCOPOLAMINE is the most effective agent for the treatment of motion sickness.

4. The newest antiemetic drug is APREPITANT, a neurokinin receptor antagonist, which may be of use in preventing the delayed phase of cancer chemotherapy induced emesis.

DRUGS YOU NEED TO KNOW (in BLUE throughout the handout):

Decontamination Agents
- ACTIVATED CHARCOAL
- IPECAC
- POLYETHYLENE GLYCOL-ELECTROLYTE SOLUTION

Antiemetic Drugs
- APREPITANT (Emend)
- DEXAMETHASONE (Decadron)
- DIMENHYDRINATE (Dramamine)
- DIPHENHYDRAMINE (Benadryl)
- DOLASETRON (Anzemet)
- DRONABINOL (Marinol)
- DROPERIDOL (Inapsine)
- GRANISETRON (Kytril)
- MECLIZINE (Antivert)
- METHYLPREDNISOLONE (Medrol)
- METOCLOPRAMIDE (Reglan)
- ONDANSETRON (Zofran)
- PROCHLORPERAZINE (Compazine)
- PROMETHAZINE (Phenergan)
- SCOPOLAMINE (TransdermScop)
LEARNING OBJECTIVES

1. Be able to describe the uses for activated charcoal and polyethylene-glycol electrolyte solution.

2. Describe the signalling processes involved in the emetic pathways, especially the receptors involved and their location relative to the blood brain barrier.

3. Explain how each **CLASS** of antiemetic agents may interrupt the emetic pathway, and **be able to provide match drugs to each class**. Know the specific indications for each type of antiemetic agent (i.e., be able to predict which agents are best used in pregnancy or to treat motion sickness or cancer chemotherapy-induced nausea and vomiting).

4. Know the therapeutic uses and side effects for **DOLASETRON, ONDANSETRON, GRANISETRON** and **APREPITANT**.

PHYSIOLOGY OF VOMITING

KEY CONCEPTS

- there are four major sites of action:

  I. Sensory receptors: in the inner ear, stomach and small intestine, and the pharynx; visual, olfactory and painful stimuli can also elicit vomiting

  II. Chemoreceptive trigger zone (CTZ) – located in the area postrema, on the floor of the 4th ventricle – OUTSIDE the blood brain barrier – primary region responsible for detection of blood-borne emetics

  III. Vomiting centre – connected to the CTZ – responsible for the initiation and coordination of the complex motor patterns needed for vomiting

  IV. “Higher centres” that are responsible for memory, fear, dread and anticipation

In determining the mechanism of action of emetic and antiemetic drugs, it is important to consider both the location of the receptors in a particular pathway, and whether the receptors are inside the blood-brain barrier.
there are 3 major types of inputs to the vomiting center to consider:

I. mechanical and/or painful stimuli especially:

**INNER EAR** (motion, aminoglycoside antibiotics) → H₁ and M receptors → cerebellum → vomiting center

**LOCAL GI IRRITATION** (cytotoxic drugs, bacteria, radiation): vagal and sympathetic afferents from the stomach and small intestine that can be modulated by the action of 5HT₃ receptors → solitary tract nucleus (5HT₃, D₂, M and H₁ receptors) **AND** the chemoreceptive trigger zone (5HT₃, D₂, M₁ receptors) → vomiting center

**PHARYNX** (gag reflex): glossopharyngeal and trigeminal afferents → solitary tract nucleus as described above

II. **BLOOD BORNE EMETICS** (esp. cytotoxic drugs, opioids, cholinomimetics, cardiac glycosides, L-Dopa, bromocriptine, apomorphine, ipecac) → chemoreceptive trigger zone (5HT₃, D₂, M₁ receptors) → vomiting center
III. “HIGHER CENTERS”: project directly to the vomiting center – especially important in the *anticipatory* nausea and vomiting that limits administration of cancer chemotherapeutics

**GI DECONTAMINATION**

**TOXIN BINDING:** *ACTIVATED CHARCOAL*

*Mechanism of action*
- adsorbs many drugs and poisons due to its large surface area
- must be given in a ratio of at least 10:1 (charcoal:toxin) by weight
- does not bind iron, lithium or potassium; binds alcohols and cyanide poorly
- not useful in cases of poisoning due to corrosive mineral acids or alkalis

**CATHARTICS:** *POLYETHYLENE GLYCOL-ELECTROLYTE SOLUTION*

*Mechanism of action*
- may hasten removal of toxins and reduce absorption (no controlled studies)
- whole bowel irrigation can enhance decontamination following ingestion of iron tablets, enteric coated medicines, illicit drug-filled packets and foreign bodies
- also used before endoscopic procedures

**EMETIC AGENT:** *IPECAC*

- use is controversial, especially if treatment is initiated more than 1 hour after ingestion of poison
- “Parents should avoid the old standby poison remedy of ipecac syrup and instead call poison control centers when children ingest toxic substances”  
  American Academy of Pediatrics, November 2003
- the FDA has stopped OTC sales of IPECAC, but it is still found in thousands of medicine cabinets
Mechanism of action

- local irritant effect as well as acting on CTZ
- emesis may not occur if stomach is empty; should be removed if emesis does not occur
- oral dose takes 15-30 minutes to effect

IPECAC should NOT be administered with activated charcoal, or if the suspected poison is corrosive, a petroleum distillate or a rapidly-acting convulsant.

ANTIEMETIC DRUGS

Types of Antiemetics

I. 5HT₃ antagonists
II. Antimuscarinics
III. NK₁ antagonist
IV. Antihistamines (H₁)
V. Dopamine (D₂) antagonists
VI. Cannabinoids
VII. Corticosteroids

I. SEROTONIN (5HT₃) ANTAGONISTS:
   DOLASETRON, ONDANSETRON, GRANISETRON

Mechanism of action

- blockade of peripheral 5HT₃ receptors on intestinal vagal afferents is thought to be primary mechanism of action, but CNS actions at both the CTZ and vomiting center are important
Therapeutic Uses

- primary agents for prevention and treatment of chemotherapy-induced nausea and vomiting – most effective in preventing acute phase (<24 hours after chemotherapy) if given 30 minutes prior to antineoplastic drugs – not particularly effective during delayed phase (2-5 days after chemotherapy)
- also used for postop and post-radiation nausea and vomiting
- restricted to vomiting related to significant vagal stimulation (e.g., poor at controlling motion sickness)

Side Effects

- well tolerated; excellent safety profiles
- most common side effects are transient, mild headache, dizziness and constipation
- cause small prolongation of QT interval (not yet shown to be clinically important)

5HT3 antagonists (esp. ONDANSETRON) are the only truly effective agents for the prevention of cancer chemotherapy induced emesis (esp. caused by cisplatin).

SCOPOLAMINE is the most effective agent for the treatment of motion sickness.

II. ANTICHOLINGERGICS: SCOPOLAMINE

Mechanism of action

- antiemetic actions mediated through inhibition of muscarinic and dopaminergic receptors in the CTZ – rapidly and fully distributed in the CNS
- very high incidence of anticholinergic effects when given orally or parenterally → give as transdermal patch
III. NEUROKININ RECEPTOR 1 (NK$_1$) ANTAGONIST: APREPITANT

**Mechanism of action**

- substance P (SP) is a neurotransmitter in both the CNS and the GI tract, and it has been implicated in nausea and vomiting – SP is the preferred ligand for the NK$_1$ tachykinin receptor
- actions are thought to be primarily central (via the CTZ)

**Therapeutic Uses**

- prevention of delayed phase of chemotherapy-induced nausea and vomiting (2-5 days after treatment), but not very effective in preventing emesis once it has begun
- given in combination with ONDANSETRON and DEXAMETHASONE

**Side Effects**

- generally well tolerated (too new to tell for sure!)
- drug-drug interactions (it’s metabolized by CYP3A4) – decreases the metabolism of warfarin, some chemotherapeutic agents (docetaxel, paclitaxel, etoposide, irinotecan, ifosfamide, imatinib, vinorelbine, vinblastine and vincristine)
- decreases effectiveness of oral contraceptives

IV. ANTIHISTAMINES (H$_1$): DIMENHYDRINATE, DIPHENHYDRAMINE, hydroxyzine, MECLIZINE, PROMETHAZINE, piperazines

**Mechanism of action**

- cause sedation (therefore older antihistamines are better antiemetics)
  (it’s debated whether all effective older antiemetics work by causing patients to fall asleep!)
- **H$_1$ receptor antagonism** may not be primary site of action (exception maybe motion sickness $\rightarrow$ vestibulocerebellar pathway) – have antimuscarinic activity
- efficacy is increased by combining with ephedrine or amphetamine
better at preventing motion sickness than stopping an episode that is already underway

Side Effects

- anticholinergic (confusion, dry mouth, urinary retention)
- possibly should not be used in pregnancy (teratogenic) – controversial
- drug interactions with certain antibiotics (terfenadine or astemizole combined with ketoconazole, itraconazole; macrolide antibiotics)

V. DOPAMINE (D₂) RECEPTOR ANTAGONISTS: DROPERIDOL, METOCLOPRAMIDE, PROCHLORPERZAINE, PROMETHAZINE

- antiemetic actions mediated through inhibition of dopaminergic (D₂) and muscarinic receptors in the CTZ
- may also facilitate “correct” pattern of GI contractions
- cause sedation via antihistaminic properties (esp. DROPERIDOL)

VI. CANNABINOIDs: DRONABINOL

- mechanism of action not understood – acts at central cannabinoid receptors
- used rarely for cancer chemotherapy-induced emesis (more effective agents are now available)
- combination therapy with phenothiazines provides synergistic antiemetic action while attenuating the adverse effects of both agents
- side effects include euphoria, dysphoria, sedation, hallucinations, dry mouth and increased appetite – occasionally causes tachycardia, conjunctival injection and orthostatic hypotension

VI. CORTICOSTEROIDS: DEXAMETHASONE, METHYLPREDNISOLONE

- unknown mechanism of action
- commonly used in combination with other agents