MED438

pharmacology
Team 438

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Antiemetic Drugs

Objectives:

By the end of the lecture , you should know:

- Classify the main different classes of antiemetic drugs according to their mechanism of action.
- Know the characteristic pharmacokinetics & dynamics of different classes of antiemetic drugs.
- Identify the selective drugs that can be used according to the cause of vomiting.
- Learn the adjuvant antiemetics.
- Describe the major side effects for the different classes of antiemetics.

Color index:

Black : Main content
Red : Important
Blue: Males' slides only
Purple: Females' slides only
Grey: Extra info or explanation
Green : Dr. notes

Editing File

Vomiting

It is a forceful expulsion of gastric contents through the mouth.
It is a **manifestation** (symptom) of many conditions and diseases.

Consequences

Dehydration | Acid-Base imbalance | Electrolyte depletion | Aspiration, pneumonia

How is it induced?

Vomiting center respond to inputs from:

01

Stimulation of chemoreceptors trigger zone (CTZ):

General info:

- CTZ is an area of medulla that communicate with vomiting center to initiate vomiting
- CTZ is physiologically **outside BBB** [1]
- CTZ contains **D2 receptors, 5-HT3 receptors & opioid receptors**

Stimulated by:

a. Emetogenic drugs (Opioids, general anesthetics, Digitalis, L-Dopa)
b. Chemicals & toxins (**blood**, **CSF**)[2]
c. Radiation
d. Uremia, estrogen (vomiting of pregnancy)

02

Disturbance of vestibular system:

a. Motion sickness (**H1 & M1 receptors**)

03

The periphery (pharynx,GIT) via sensory nerves:

a. GIT irritation
b. Myocardial infarction
c. Renal or biliary stones

04

Higher cortical centers stimulation(CNS):

a. Emotional factors
b. Nauseating smells or sights

Chemical transmitters & receptors involved in vomiting and drug targets:

- Ach (Muscarinic receptors)
- Histamine (H1)
- Substance P (Neurokinin receptors, NK1)
- Dopamine (D2)
- Serotonin (5-HT3)
- Opioid (Opioid receptors)

1) Responds to chemical changes in both the blood and the CSF.
2) Gastroenteritis releases toxins into the blood circulation which can stimulate the CTZ.

Pathophysiology of Emesis:

★ Receptors and their location are important

2.Pharynx & GIT:
5-HT3 receptors.
Triggered by:
- Chemo & radiotherapy
- Gastroenteritis

1.Cerebral cortex

Triggered by:
- Smell
- Sight
- Thought
- anticipatory emesis

Vomiting center (medulla)
Receptor:
Muscarinic, 5-HT3

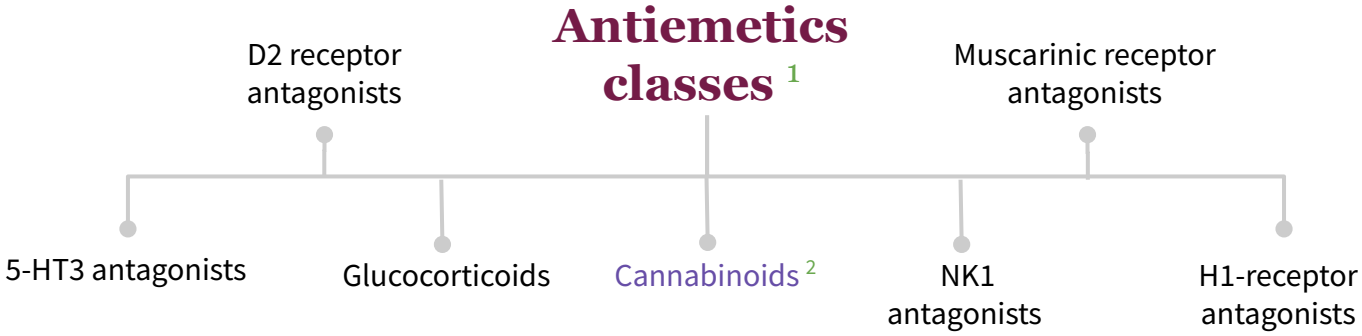
3.Chemoreceptors trigger zone
(outside BBB)
- 5-HT3
- Dopamine D2
- Opioid receptor
- Substance P

Triggered by:
- Chemotherapy
- Opioids
- Anesthetics

4.Vestibular nuclei:
- Muscarinic M1
- Histaminic H1.

Triggered by:
- Motion sickness

Antiemetics classes [1]



Serotonin (5-HT3) antagonists

Drug	Ondansetron	Granisetron
M.O.A	• Act by blocking 5-HT3 receptor **centrally** (in vomiting center, CTZ) and **peripherally** (5HT3 receptors on GI vagal afferents).	
P.K	• Orally or parenterally • Have long duration of action, first pass effect ★ The **most potent** antiemetic drugs	
Uses	★ **First choice** for prevention of moderate to severe emesis: ○ Chemotherapy-induced nausea and vomiting (CINV) especially **cisplatin**[3]. ○ Post-radiation NV & Post-operative NV. ★ Their effects are augmented by **combination** with corticosteroids and NK1 antagonists[4]	
ADRs	They are well tolerated in general [5] • Headache, dizziness and constipation. • Minor ECG abnormalities (QT prolongation)	

1) 5-HT3 antagonists, D2 antagonists and NK1 antagonists are the most clinically used classes.
2) Euphoria and addiction liability with cannabinoids is high thus not used clinically.
3) Highly emetogenic anticancer drug.
4) Using 5-HT3 antagonists alone is effective, but using it in triple therapy produces the most effective antiemetic effect for cancer induced nausea and vomiting.
5) blocking of 5-HT3 may lead to the blockade of 5-HT4 receptors, which will result in the mentioned ADRs.

D2 receptor antagonists (Block D2 dopamine receptors in the CTZ)

- **Prokinetics drugs** [1]
- **Neuroleptics (antipsychotics)**

A) Prokinetic D2 receptor antagonists

Drug	Domperidone	Metoclopramide
M.O.A	• Blocks D2 Dopamine receptors in the CTZ (both drugs have antiemetic effects as CTZ is outside the blood brain barrier). ★ They are prokinetic agents (**5HT4 agonist activity**): **Increases upper GI motility and gastric emptying**	
P.K	• Given orally. • Does not cross BBB	• Given orally Or IV. • Cross BBB
Uses	**Antiemetic action (due to blocking D2 receptor in CTZ):** • Effective against vomiting due to cytotoxic drugs, gastroenteritis, surgery, toxins, uremia, radiation. **Prokinetic action (due to 5HT4 agonist activity):** • Used in Gastroesophageal reflux disease (GERD) ★ Used in gastroparesis (impaired gastric emptying after surgery) [2]	
ADRs	**Only for Metoclopramide:** • Dyskinesia (extrapyramidal side effects) • Galactorrhea, menstrual disorders, impotence • Postural hypotension (α- blocking action) • Sedation, drowsiness	

B) D2 receptor antagonists Neuroleptics (Antipsychotics)[3]

Drug	Chlorpromazine (CPZ)	Droperidol
Uses	• Postoperative vomiting • Chemotherapy-induced emesis	
ADRs	• Extrapyramidal symptoms • Sedation • Postural hypotension (alpha blocking effect)	

1) A prokinetic agent is a type of drug which enhances gastrointestinal motility by increasing the frequency or strength of contractions, but without disrupting their rhythm.
2) Can be used with diabetics to treat Gastroparesis caused by neuropathy.
3) Not first line

Neurokinin-1 (NK1) receptor antagonists

Drug	Aprepitant
M.O.A	★ Acts centrally as **substance P antagonist** by blocking neurokinin-1 receptors in vagal afferent fibers.
P.K	• Orally.
Uses	★ Usually combined with 5-HT3 antagonists and corticosteroids in prevention of chemotherapy-induced nausea and vomiting and post-operative NV. [1]

H1-receptor antagonists

Drug	Diphenhydramine | Promethazine | Meclizine | Cyclizine
Uses	• Motion sickness • Morning sickness in pregnancy • Promethazine: Severe morning sickness of pregnancy (only if essential)
ADRs	• Prominent sedation. • Hypotension. (alpha blocking effect) • Anticholinergic effects or atropine like actions (dry mouth, dilated pupils, urinary retention, constipation)

Muscarinic receptor antagonists

Drug	Hyoscine (Scopolamine)
M.O.A	• Reduces impulses from vestibular apparatus
P.K	• Orally, injection, patches
Uses	• Used as transdermal patches in **motion sickness** (applied behind the external ear) ★ Not in chemotherapy-induced vomiting

ADRs	• Sedation
	• Atropine like actions:
	  ○ Blurred vision
	  ○ Tachycardia
	  ○ Dry mouth
	  ○ Constipation
	  ○ Urinary retention

1) It is not strong enough to be given alone as antiemetic drug, so other drugs of different action must be given too.

Glucocorticoids [1]

Drug	Dexamethasone	Methylprednisolone
Uses	• Used in chemotherapy-induced vomiting • Combined with 5-HT3 antagonists or NK1 receptor antagonist	
ADRs	• Hypertension [2] • Hyperglycemia • Cataract • Osteoporosis • Increased intraocular pressure • Increased susceptibility to infection • Increased appetite & obesity.	

Summary

The choice of antiemetic depends on the etiology:

Motion sickness:

- Muscarinic antagonists
- Antihistamines

Vomiting with pregnancy (morning sickness):

- Avoid all drugs in the first trimester
- Pyridoxine (B6)[3]
- Promethazine (late pregnancy).

Vomiting due to cytotoxic drugs:

- 5-HT3 antagonists
- NK1 antagonists
- D2- antagonists
- Glucocorticoids

Post operative nausea & vomiting:

- Dopamine antagonists

Drug- induced vomiting (CTZ), uremia, gastritis:

- Dopamine antagonists

Doctor Notes:

- **Severe nausea and vomiting** -----> Glucocorticoids, Serotonin (5-HT3) antagonists
- **Severe nausea and vomiting due to migraine** ------> Diphenhydramine
- **Severe nausea and vomiting due to infection?**
  A) Diphenhydramine B) chlorpromazine C)scopolamine D) NK1 antagonist

Answer is : A , B also answer , but (A) is safer and 1st line is ondansetron, if was there is instead of (A) , then ondansetron is the choice because it's safer than chlorpromazine

- **Motion sickness**-----> Scopolamine
- **Morning sickness** ------> H1-receptor antagonists
- If have a patient on H1 blocker and it didn't work and you want to add a drug , you add Serotonin (5-HT3) antagonists

1) It's unknown how Glucocorticoids produce an antiemetic effect.
2) Because cortisone is involved in regulating the body's balance of water, sodium, and other electrolytes, using these drugs can promote fluid retention and sometimes cause or worsen high blood pressure.
3) Vitamin B6 (pyridoxine) supplementation during pregnancy may provide some relief from pregnancy-related nausea.

Quiz

MCQ

1- A 42 year old cancer patient on chemotherapy developed severe nausea and vomiting. what is the drug of choice?

A)Dexamethasone
B)Ondansetron
C)Domperidone
D)Meclizine

2- A patient was prescribed an antiemetic that caused extrapyramidal side effects, Galactorrhea,Sedation. what is the given drug?

A)Domperidone
B)Diphenhydramine
C)Metoclopramide
D)Hyoscine

3- A Pregnant patient with severe motion sickness was given an antiemetic drug, then developed dry mouth, dilated pupils, hypotension. what is the given drug?

A)Scopolamine
B)Droperidol
C)Aprepitant
D)Promethazine

4- A cancer patient was prescribed a drug for his vomiting, he then developed Hyperglycemia and Osteoporosis.what is the drug prescribed?

A)Methylprednisolone
B)Metoclopramide
C) Granisetron
D)Cyclizine

5- A patient came to the clinic suffering from motion sickness, he was prescribed a drug that caused Tachycardia. what is the drug?

A) Dexamethasone
B)Hyoscine
C)Aprepitant
D)Domperidone

SAQ

A 58 years old patient on chemotherapy came to the hospital due to having nausea and vomiting. The doctor gave him ondansetron and Aprepitant .

Q1- what is the MOA of Ondansetron?
Q2- write 3 ADRs for Ondansetron.
Q3- why the doctor gave him Aprepitant ?
Q4- Mention another Class of drugs that can be combined with Ondansetron .
Q5- Mention 4 ADRs for the class of drugs mentioned in Q4.

Answers:

MCQ

Q1	B
Q2	C
Q3	D
Q4	A
Q5	B

SAQ

Q1	Act by blocking 5-HT3 receptor centrally (in vomiting center, CTZ) and peripherally (5HT3 receptors on GI vagal afferents).
Q2	Headache,constipation,Minor ECG abnormalities
Q3	prevention of chemotherapy-induced nausea and vomiting
Q4	Glucocorticoids
Q5	Hypertension,Hyperglycemia,Cataract,Osteoporosis,increased appetite & obesity.

Share with us your ideas !

Good Luck , Future Doctors!

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