

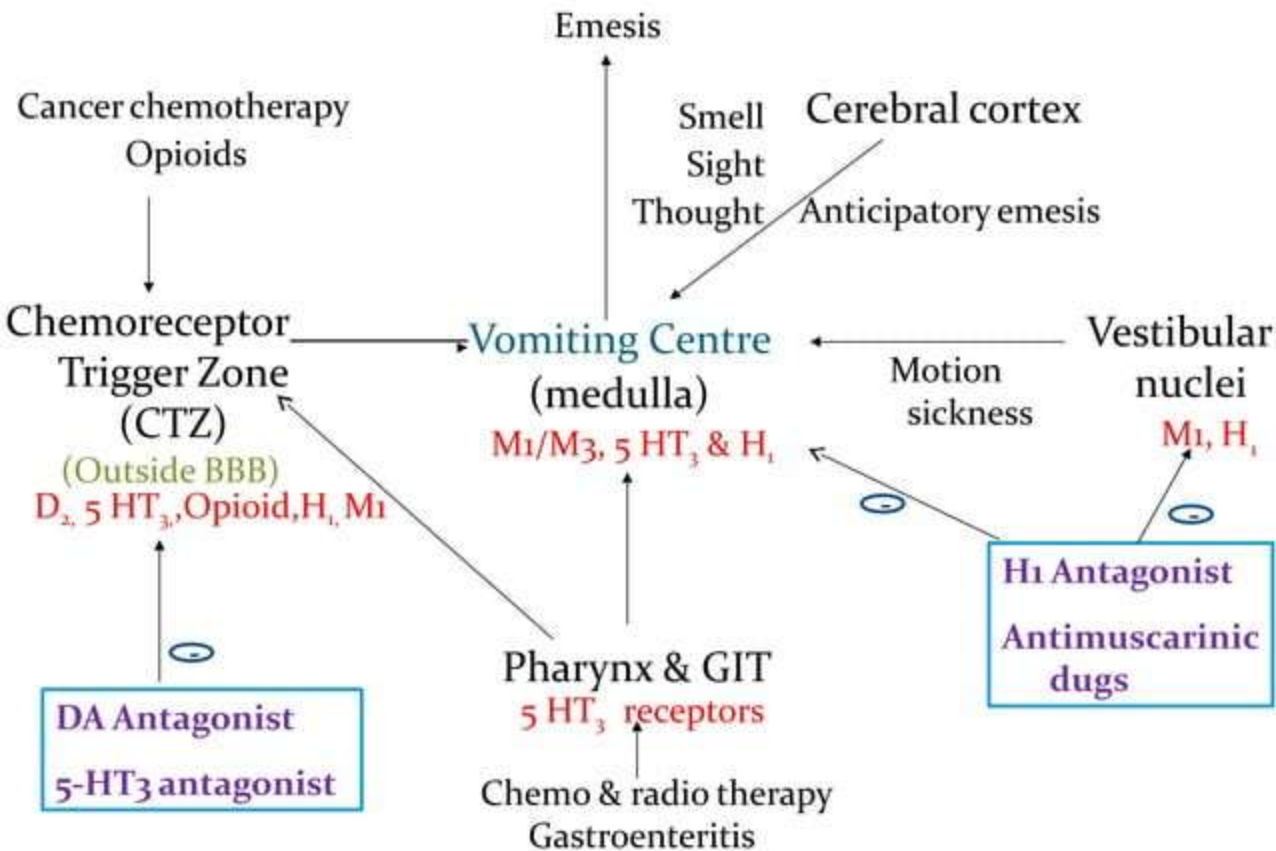
EMETICS AND ANTI-EMETICS

DR. SSEKAWU CHARLES

Emesis

- Is a protective mechanism which serves to eliminate harmful substances from the stomach and duodenum
- Occurs due to stimulation of the emetic center situated in the medulla oblongata
- Multiple pathways can elicit vomiting
 - CTZ (The chemoreceptor Trigger Zone) in the areas of postrema
 - NTS (The Nucleus Tractus Solitarius)
- are the most important relay areas for afferent impulses arising from GIT, throat and other viscera
- CTZ is also accessible to blood borne drugs, mediators, hormones, toxins etc.,
- bse its not protected by the blood brain barriers

Pathophysiology of Emesis



Receptor of CTZ and NTS through emetic signal are relayed

- Histamine (H1)
- Cholinergic (M)
- Dopamine (D2)
- Serotonin 5HT3
- Cannabinoid (CBI)
- Opioid (μ) receptors
- Neurokinin (NK1) activated by substance p

Dopamine

Hormones
Azotaemia
Diabetes

Opioids
Chemotherapy
Anaesthetics



5-HT₃

BBB

Acetylcholine

Vestibular
Sights
Smell
Taste

Emetic Centre

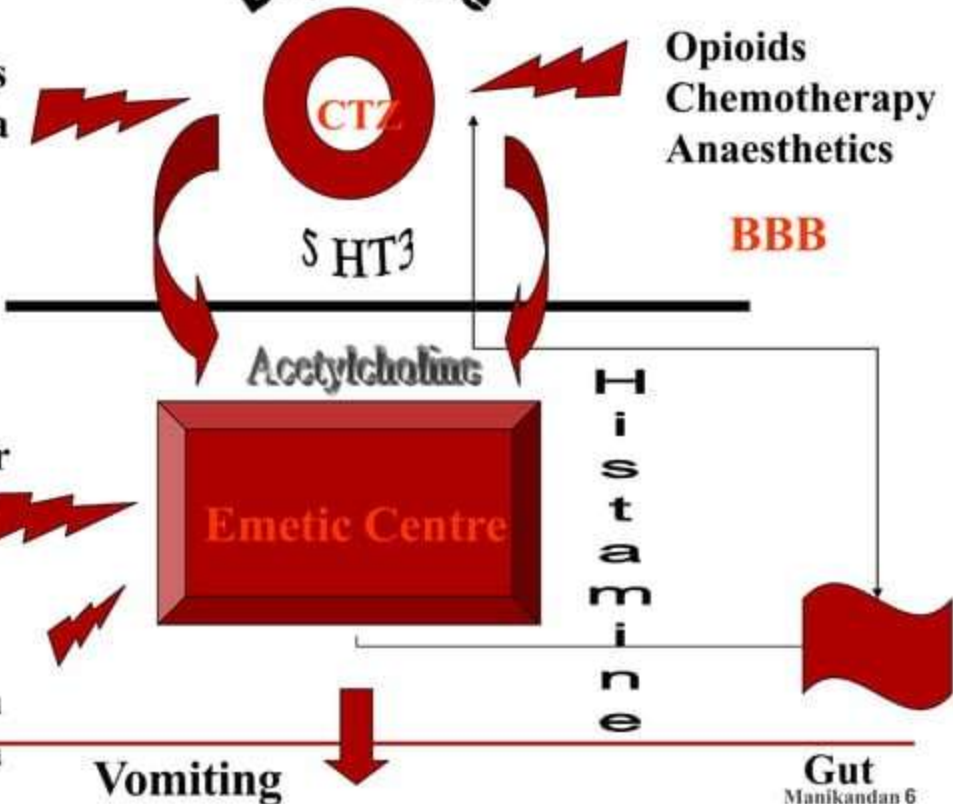
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Hypotension
Hypoxaemia

Vomiting

Gut

Manikandan 6



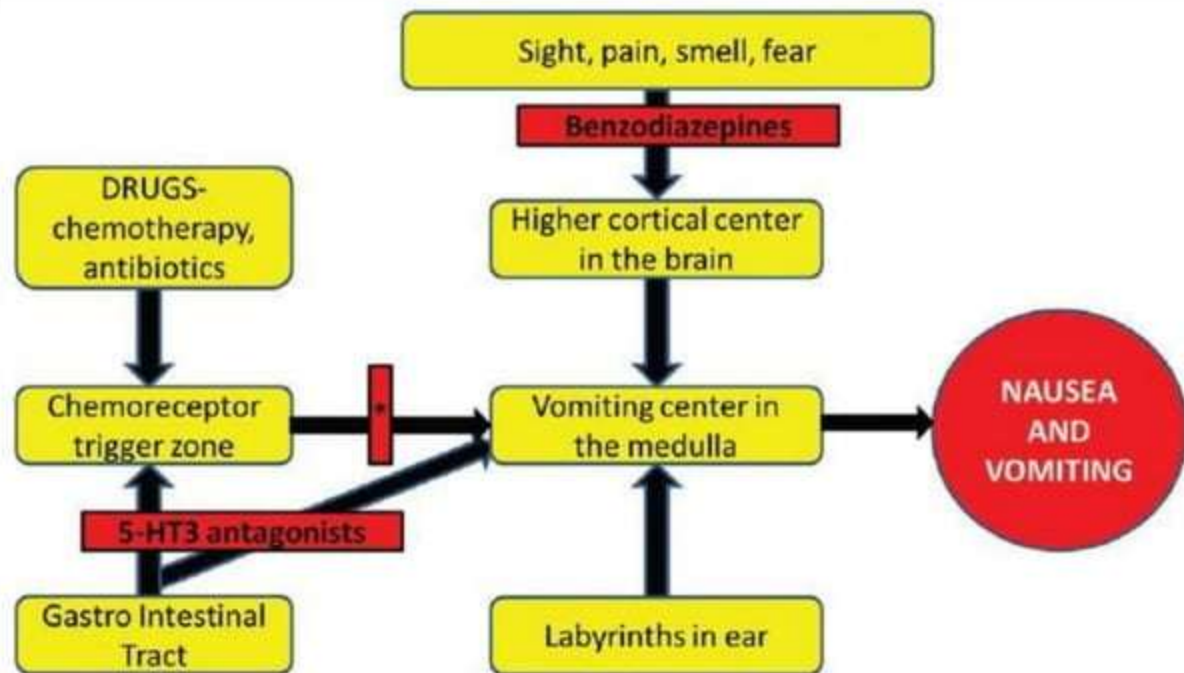
VOMITING RESPONSE

Generation of Signal (impulses, stimuli :
Severe pain
Bad odour
Gasty sight
Fear
Recall of abnoxious event

Vomiting
centre

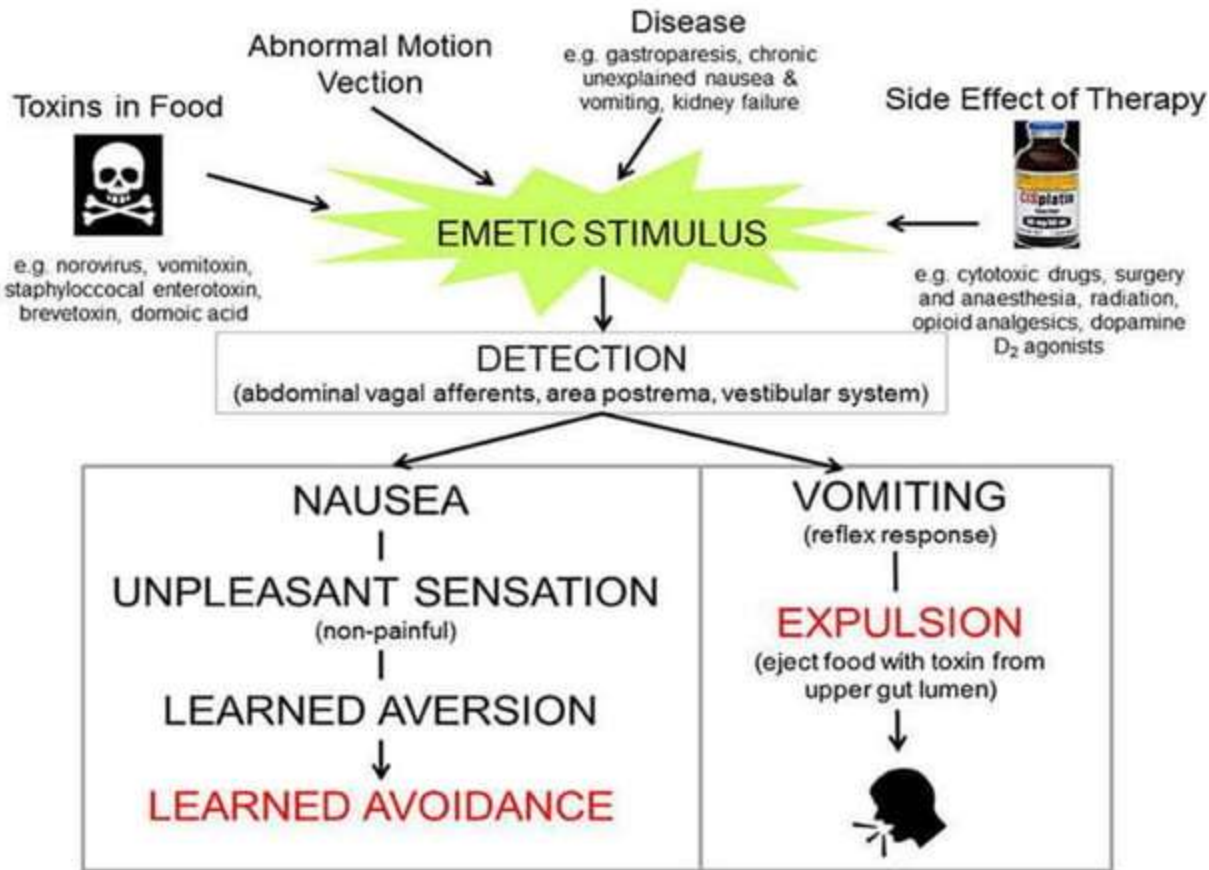
Nausea and
vomiiting

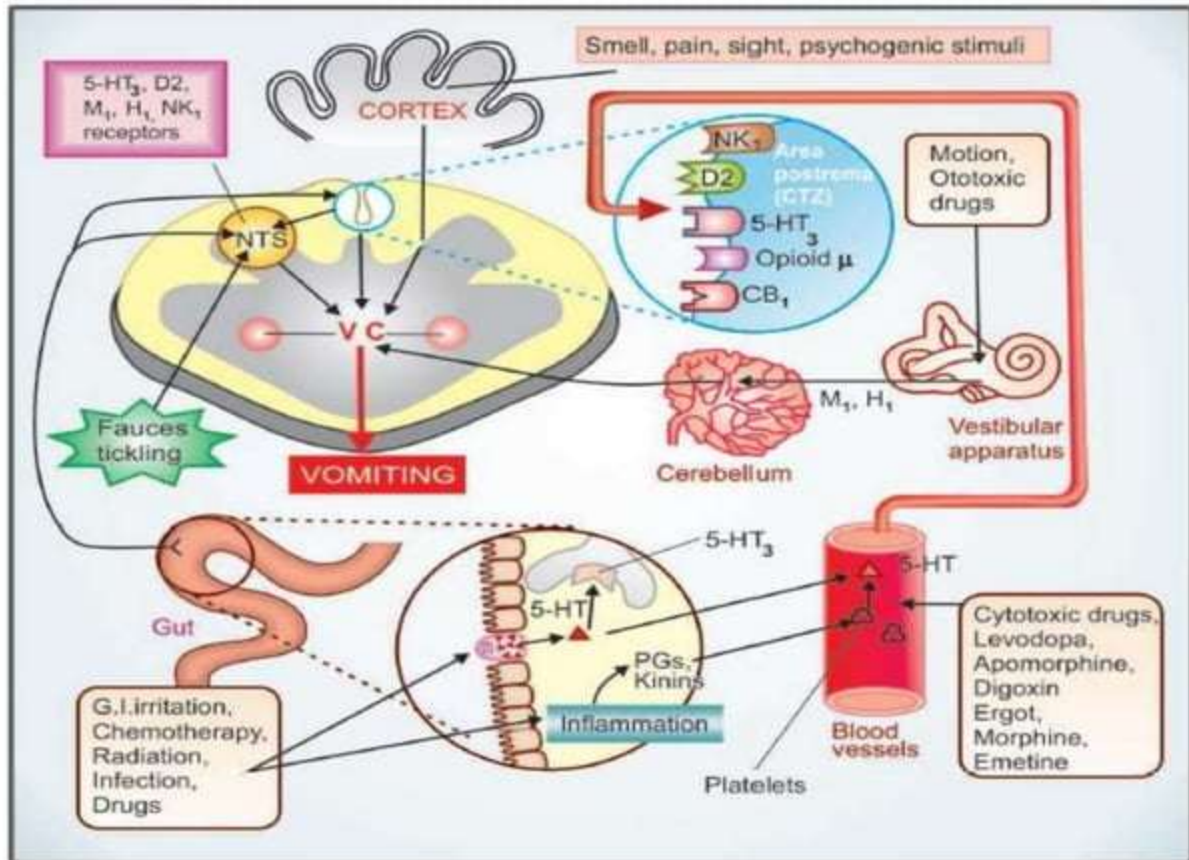
- Nausea – accompanied by reduced gastric tone and peristalsis
- Emetic response
 - Body of the stomach, Esophageal sphincter and Esophagus Relax
 - Duodenum and pyloric stomach contracts in retrograde manners
 - Rhythmic contraction of diaphragm and abdominal muscles compresses the stomach
 - Content evacuated via the mouth
 - Conditions that inhibits gastric emptying predispose to vomiting



* Histamine, Dopamine and Muscarinic antagonists, Cannabinoids

→ Site of action of drugs





Emetics

- **Centrally acting:** Apomorphine and morphine
 - directly stimulate the CTZ or VC
- **Reflexly acting:** Ipecacuanha
 - stimulate the VC by irritating gastric & duodenal mucosa which stimulate afferent fibres of vagus nerve
- **Locally acting:** Aluminum, Sodium Chloride (Concentrated Solution)
- **Other Drugs as Adverse Effect:** Morphine, Digitalis, Emetine, Aspirin, Quinine & Anticancer drugs

Emetics –centrally acting

Apomorphine:

- Given SC/IM -6mg
- Causes vomiting within 15 min
- In hypersensitive individuals, however, even a subtherapeutic dose may elicit severe emesis and collapse
- Vomiting is often accompanied by sedation
- It should not be used if respiration is depressed
- Large doses often produce restlessness, tremors, occasionally convulsions
- Sometimes may cause hypotension, syncope and coma

Emetics –peripherally acting

Mustard:

- Volatile oil
- Formed as a result of a reaction between a glycoside and an enzyme in the presence of water
- It is safe and easily available
- Dose -1 tp in water

Sodium chloride:

- Given orally
- Withdraws fluid from the cells lining the stomach thus causes irritation which causes reflex emesis

Emetics –both

Ipecacuanha (Emetine):

- Acts by irritating gastric mucosa as well as through CTZ
- Dried root of *Cephalis ipecacuanha* contains emetine
- Used as *syrup ipecac* (15-20ml adults, 10-15ml children, 5ml in infants) for inducing vomiting
- Takes 15 min or more for the effect

Emetics –contraindication

All emetics contraindicated in;

- Corrosive (alkali, acid) poisoning: there is risk of perforation and further injury to esophageal
- CNS stimulant drug poisoning: bse they may precipitate convulsion
- Kerosine (petroleum) poisoning: risk of aspiration of liquids due low viscosity and chemical pneumonia
- Unconscious patient: may aspirate vomitus bse of laryngeal reflex is impaired
- Morphine or phenothiazone poisoning b'se of emetic may fail to act

List of Drugs induce vomiting

- Anticancer drugs
- Amiodarone
- Apomorphine
- Chloroquine, quinine
- Diltiazem
- Emetine
- Ergot derivatives
- Erythromycin, tetracyclines
- Fluroquinolones
- Metronidazole

Antiemetics

Classification:

1. Anticholinergics:

Hyoscine, Dicyclomine

2. H₁ antihistaminics:

*Promethazine, Diphenhydramine, Cyclizine,
Meclozine, Cinnarizine*

3. Neuroleptics:

*Chlorpromazine, Prochlorperazine, Haloperidol,
etc.*

4. Prokinetic drugs:

*Metoclopramide, Domperidone, Cisapride,
Mosapride*

5. 5HT₃-Antagonists:

Ondansetron, Granisetron, Dolasetron

6. Adjuvant antiemetics:

Corticosteroids, Benzodiazepines, Cannabinoids

ANTIEMETICS

Anticholinergics

Hyoscine
Dicyclomine

Neuroleptics (D2 blockers)

Chlorpromazine
Triflupromazine
Prochlorperazine
(others)

Prokinetic drugs

Metoclopramide
Domperidone
Cisapride,
Mosapride
Itopride
Levosulpiride
Cinitapride

NK₁ receptor antagonists

Aprepitant
Fosaprepitant

H₁ antihistaminics

Promethazine
Diphenhydramine
Dimenhydrinate
Doxylamine
Meclizine (Meclizine)

5-HT₃ antagonists

Ondansetron
Granisetron
Palonosetron
Ramosetron

Adjuvant antiemetics

Dexamethasone
Benzodiazepines
Dronabinol

Anticholinergics

Hyoscine:

- Most effective for motion sickness
- 0.2 -0.4mg oral, i.m
- Brief duration of action
- Produces sedation and other anticholinergic side effects
- Antiemetic action is exerted blocking conduction of nerve impulses across a cholinergic link in the pathway leading from the vestibular apparatus to the vomiting centre
- Suitable for short risk journeys
- It has poor efficacy in vomiting
- Transdermal patch 1.5mg applied behind the pinna –to be delivered over 3 days –suppresses motion sickness while producing only mild side effects

Anticholinergics

Cont...

Dicyclomine:

- 10-20mg oral
- Used for prophylaxis of motion sickness and for morning sickness
- It has been cleared of teratogenic potential

H₁ antihistaminics

- Some antihistaminics are antiemetic
- They are useful mainly in motion sickness and lesser extent in morning sickness, postoperative and some other forms of vomiting
- Their antiemetic effect appears to be based on anticholinergic, antihistaminic and sedative properties
- Drugs available
 1. Meclizine
 2. Cyclizine
 3. Dimenhydrinate
 4. Diphenhydramine
 5. Promethazine – *Used in pregnancy, used by NASA for space motion sickness*

Promethazine, diphenhydramine, dimenhydrinate

- Afford protection from motion sickness for 4-6 hours
- Produce sedation and dryness of mouth
- Driving is not after taking anti motion sickness drugs
- Block extrapyramidal side effects of metoclopramide while supplementing its antiemetic action.

Doxylamine

- It's a sedative H1 antihistamine with prominent anticholinergic activity
- Used for morning sickness in combination with pyridoxine
- Side effects are
 - Drowsiness
 - Dry mouth
 - vertigo
 - Abdominal upset

Cinnarizine

- Its an antivertigo drug with antimotion sickness property
- It act by inhibiting influx of calcium ions from endolymph into the vestibular sensory

H₁ antihistaminics

Cont..

- All antimotion drugs are more effective when taken ½ -1 hr before commencing journey
- Motion sickness Atiemetics with anticholinergic property are the first choice
- Once sickness has started, it is more difficult to control

Neuroleptics

- Potent antiemetics
- Act by *blocking D₂ receptors in the CTZ*
- Antagonize apomorphine induced vomiting
- Antiemetic dose is much lower than antipsychotic doses
- These agents should not be administered until the cause of vomiting has been diagnosed

Neuroleptics

Cont...

- Broad spectrum antiemetic, effective in:
 - Drug induced and postanesthetic nausea and vomiting
 - Disease induced vomiting
 - Chemotherapy induced (mildly emetogenic)
 - Morning sickness: should not be used except in hyperemesis gravidarum

Prokinetic drugs

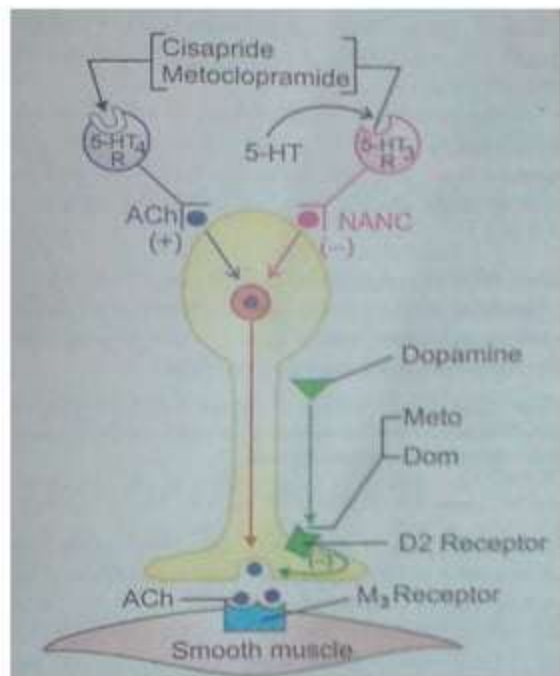
- Promote GI transit and speed gastric emptying
- Drugs available

Metoclopramide

Domperidone

Cisapride

Mechanism of action of Prokinetic Drugs



- D₂antagonism
- 5-HT₄agonism
- 5-HT₃antagonism

Prokinetic drugs

Cont...

Metoclopramide

- Introduced in early 1970s as a 'gastric hurrying agent'
- Widely used antiemetic

Actions:

GIT

CNS

Prokinetic drugs

Cont...

Interactions:

- Hastens absorption of many drugs:
 - Aspirin,
 - Diazepam etc. by facilitating the gastric emptying
- Reduces absorption of digoxin

Prokinetic drugs

Cont...

Adverse effects:

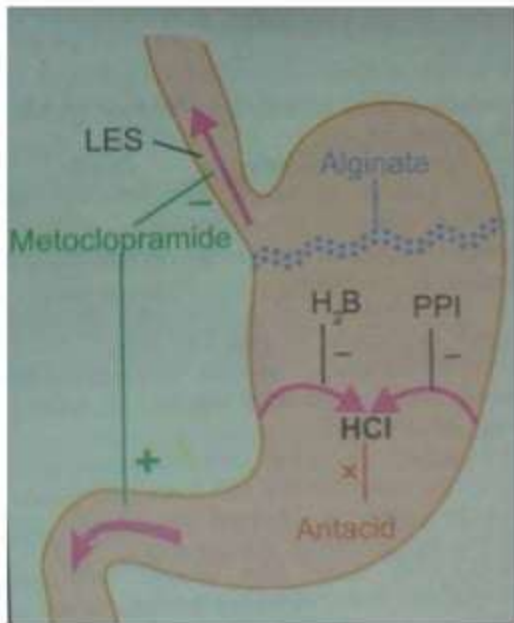
- Well tolerated
- Sedation, dizziness, diarrhoea, muscle dystonias
- Long term use can cause parkinsonism, galactorrhoea and gynaecomastia

Prokinetic drugs

Cont...

Uses:

- Antiemetic
- Gastrokinetic
- Dyspepsia
- Gastroesophageal reflux disease



Prokinetic drugs

Cont...

Domperidone:

- D₂ antagonist
- Chemically related to haloperidol but pharmacologically related to metoclopramide
- Has lower ceiling antiemetic and prokinetic actions
- Poorly crosses BBB
- Rare extra pyramidal side effects
- Given with levodopa or bromocriptine to counteract their dose limiting emetic action

Prokinetic drugs

Cont...

- Absorbed orally, but bioavailability is only 15% due to first pass metabolism
- Completely metabolized and excreted in urine
- $t_{1/2}$ is 7.5hr
- Side effects are less than with metoclopramide
 - *Dry mouth,*
 - *Loose stools*
 - *Headache*
 - *Rashes*
 - *Galactorrhoea*
 - *Cardiac arrhythmias on rapid i.v. injection*

Prokinetic drugs

Cont...

Which is a better antiemetic – Metoclopramide or Domperidone ?

- As CTZ is outside BBB both have antiemetic effects.
- But as metoclopramide crosses BBB it has adverse effects like extrapyramidal side effects..
- Domperidone is well tolerated

Prokinetic drugs

Cont...

Cisapride:

- Prokinetic drug with little antiemetic property, because it lacks D2 receptor antagonism
- Gastric emptying is accelerated
- LES tone is improved, esophageal peristalsis augmented
- Devoid of action on CTZ and does not produce extrapyramidal symptoms
- *Primary indication of cisapride has been GERD*

5-HT₃ antagonists

- Potent antiemetics
- Even though 5 HT₃ receptors are present in vomiting centre & CTZ, the antiemetic action is restricted to emesis caused by vagal stimulation.
- 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.

5-HT₃ antagonists

Cont...

- Ondansetron 32 mg / day
- Granisetron 10 µg / kg / day
- Dolasetron 1.8 mg / kg / day

Indications

- Chemotherapy induced nausea & vomiting – given 30 min. before chemotherapy.
- Postoperative & postradiation nausea & vomiting

5-HT₃ antagonists

Cont...

Adverse Effects

- Excellent safety profile
- Headache & constipation (common side effect)
- All three drugs cause prolongation of QT interval, but more pronounced with dolasetron.

Adjuvant antiemetics

1. Corticosteroids
2. Benzodiazepines
3. Cannabinoids:
 - Active principle of the *cannabis indica*
 - Possesses antiemetic efficacy against moderately emetogenic chemotherapy
 - Dronabinol – used as adjuvant in chemotherapy induced vomiting. It is a psychoactive substance.
 - Nabilone – chemotherapy induced nausea and vomiting, used under close observation, neurological adverse effects