EMESIS

→ Emesis / vomiting occurs due to stimulation of the emetic (vomiting) centre situated in the medulla oblongata.

↓

→ fundus and body of stomach, esophageal sphincter and esophagus relax., glottis closes.

↓

while duodenum and pyloric stomach contract ~~contract~~ in retrograde manner

↓

Rhythmic contractions of diaphragm and abdominal muscles then compresses the stomach

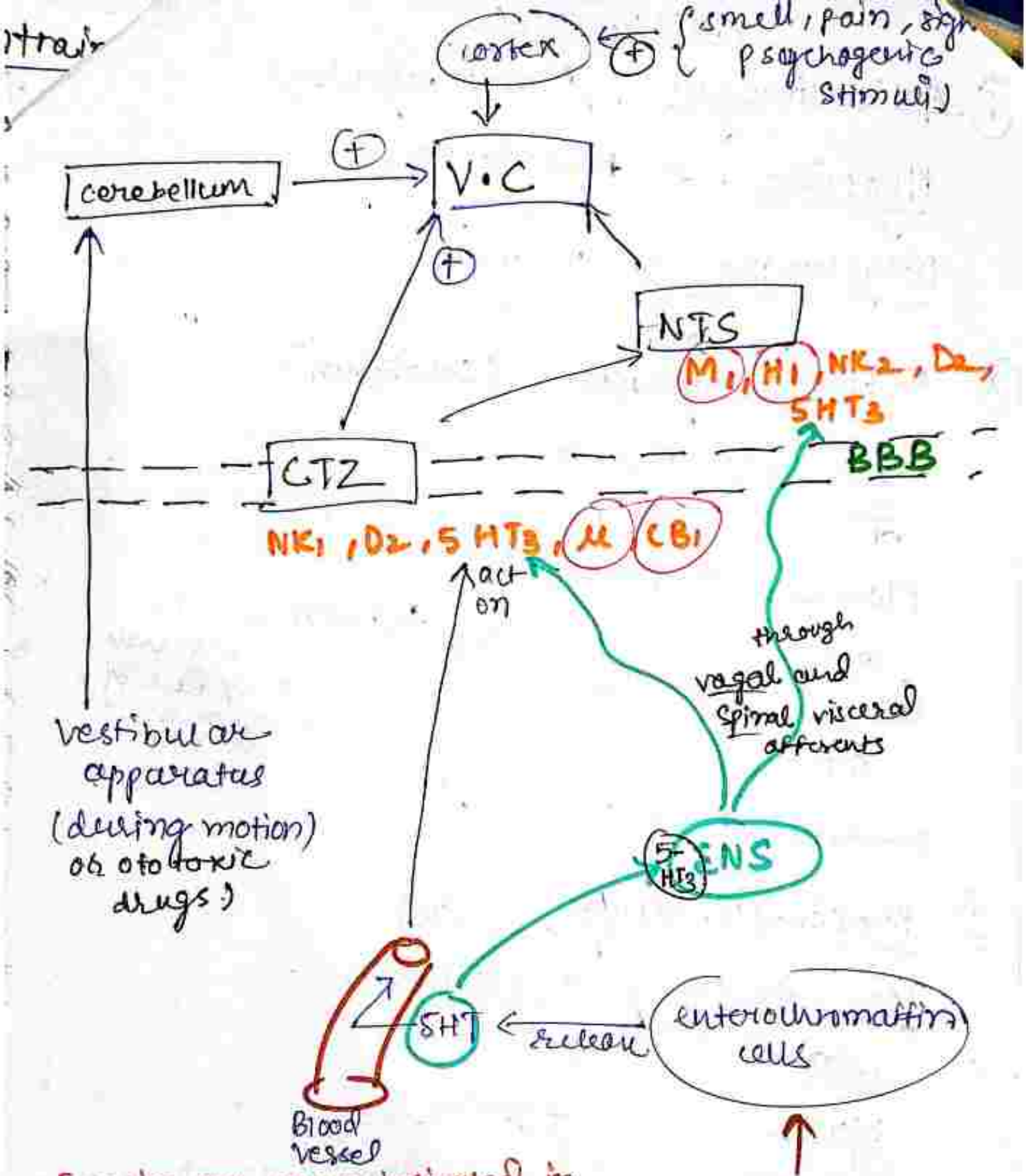
↓

evacuate its contents via the mouth.

→ **protective reflex that help to remove toxic substances.**

Drugs used for vomiting :-

- Mustard
- common salt
- Apomorphine
- Ipecac



Emetics are contraindicated in

(a) CORROSIVE (ACID/ALKALI) POISONING

(b) CNS stimulant drug poisoning.

(c) kerosine (petroleum) poisoning

(d) unconscious patient

(e) MORPHINE OR PENOTHIAZINE POISONING

ANTI-EMETICS

- Anti-cholinergics (M1 antagonist)
  - Hyascine
  - Dicyclomine
- 5-HT3 antagonists
  - Ramo, Palono, Grani → setron
  - Ondan
- Prokinetic drugs
  - Metoclopramide
  - Itopride: Itamosa, Cisapride, Cinitapride
  - Levosulpiride
  - Domperidone
- Neuroleptics (D2 blockers)
  - Trifluoperazine
  - Chlorpromazine
  - Prochlorperazine
  - Haloperidol
- H1-antihistamine
  - Cinnarizine
  - Dimenhydrinate
  - Diphenhydramine
  - Cyclizine
  - Promethazine
  - Meclizine
- NK1 receptor
  - Aprepitant
  - Fosaprepitant
- Adjuvant anti-emetic
  - Dronabinol
  - Benzodiazepine
  - Dexamethasone

ANTIEMETICS

① Anticholinergics (M1 antagonist)

Hyoscine → Hya busa
↓
Dicyclomine → Di cycle

② 5-HT3 antagonists (serotonin)

Ram → Ramo
ने
Plane → Palono
गर्ल
Grani → Grani
गर्ल
~~on do~~ गेला → On dan

} D.O.C for chemotherapy Induced vomiting

Setron used in pregnancy only case of hyperemesis gravidarum

③ Prokinetic drugs. (5-HT4) → promote GIT transit, speed gastric emptying

H1
H2
H3
H4

Me toclo + pramide

- Ito
- Mosa
- cisa
- cinita

} pride

levo sulpiride

Dompesidone (Structure related to haloperidol)

Neuroleptics (D_2 blockers) #

Tri flu → pro mazine

Chlor pro mazine

pro chlor perazine → phenothiazine

Halo peri dol

(5) H1 - anti-histamine → used for vertigo

Cinnarizine

Dimen + hydrinate

Diphen + hydramine

cyclizine

Promethazine

Meclizine

scenery
gt men
gt phen

(6) NK1 receptor antagonist

Aprepitant — Aap → repeate

fosa + Aprepitant

(7) Adjuvant anti-emetics

Dronabinol → 52 na bina

Dexamethasone

Benzodiazepines (BZDs)

Anticholinergics → Hyoscine, Dicyclomine

- Scopolamine (Hyoscine) is the drug of choice to prevent motion sickness.
- oral, i.m, transdermal patches behind the ear pinna (to reduce side effects)

M.O.A

blocking conduction of nerve impulses across a cholinergic link in the pathway leading from the vestibular apparatus to the vomiting centre.

- Other drugs used → Dicyclomine, Promethazine, cyclizine
- Travelling → vestibular stimulation, psychological factors, environmental factors.
- side effects :- dry mouth, sedation, other anticholinergic side effects.

Dicyclomine :- prophylaxis → motion sickness, morning sickness

→ tetratogenic potential

H_2 - antihistaminics

- Mainly useful for the prevention of motion sickness.
- lesser extent morning sickness, post-operative and other types of vomiting.

Promethazine
Dimen hydrinate
Diphen hydramine
} motion sickness → but produce sedation and dry mouth
4-6 hrs

Doxylamine + pyridoxine → in india for morning sickness (vomiting of early pregnancy).

side effects
- drowsiness
- dry mouth
- vertigo.

Meclozine:- against sea sickness.
→ less sedative, less anti-cholinergic and longer-acting (24 hour).

Cinnarizine: anti-vertigo drug.
act by inhibiting ca^{2+} influx
endolymph ——| ——→ vestibular sensory cells ↓ labyrinthine reflexes

MOTION SICKNESS

Anti-cholinergics, Anti-histamine } → first choice drugs for motion sickness.

Anti-dopaminergic, 5-HT3 } → less effective

→ should taken before 0.5 - 1 hour before

NEUROLEPTICS (block D_2 receptor in CTZ)

- potent anti-emetics and sedative.
- Broad spectrum anti-emetics.

↓ PONV → ↓ apomorphine
↓ Disease induced
↓ malignancy induced
↓ Radiation sickness
↓ morning sickness

A·D → muscular dystonia and EPS

PROCHLORPERAZINE

- D_2-blocking phenothiazine labrinthine suppressant
- selective antivertigo and antiemetic actions
  - ↓ injection
  - ↓ CINV
- not used as anti-psychotic (Anti-emetic)

A·D·E :- sedation.
muscle dystonia
other extrapyramidal symptoms.
dryness of mouth.

PROKINETIC DRUGS

- promote g·I transit
- speed gastric emptying

} by enhancing co-ordinated propulsive motility

- **Ach (Acetycholine) major neurotransmitter in the G·I·T for peristaltic movement**

D2 → both inhibits release of Ach

5-HT3 → both inhibits release of Ach

5-HT4 → increase the release of Ach

we need to antagonize D2 and 5-HT3

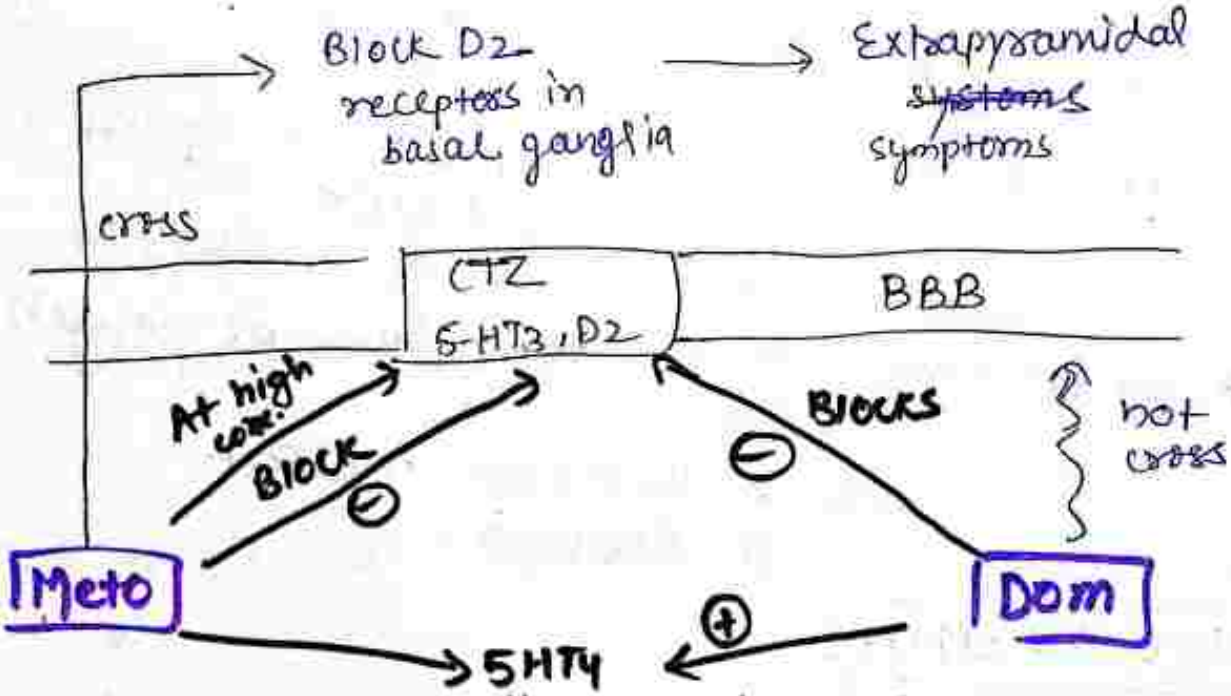
↑ agonize 5-HT4

for increase peristalysis

Imp.

Cholinomimetics and anti-ChEs not used here bcoz produce tonic and largely un-coordinated contraction.

Metoclopramide → substituted benzamide



↑ tone LES

Relax pyloric sphincter and duodenum bulb

↑ses the peristaltic movement

$D_2 \propto \frac{1}{\text{prolactin}}$ $GIT \propto \frac{1}{\text{prolactin}}$

Metoclopramide

Higher doses

- Blocks D_2 receptors
  - CNS
    - ↑ prolactin → Gynaecomastia, Galactorrhoea
    - EPS
  - CTZ → Anti-emetic
  - Gut → ↑ LES tone, hasten gastric emptying → prokinetic effect
- 5-HT4 agonist → ↑ Ach release in gut → prokinetic effect
- Blocks 5-HT3 receptors

prokinetic effect block by atropine

DRUG INTERACTIONS

→ rate of absorption of aspirin, diazepam, digoxin ↓ ses

→ By blocking DA receptors in basal ganglia ↓ abolish therapeutic effect of levodopa.

not used in PD

ADVERSE EFFECTS

- sedation, dizziness
- loose stools
- muscle dystonia (in children)
- parkinsonism, galactorrhoea and gynaecomastia

- Anti-emetic
  - used for CINV (cisplatin)
  - Promethazine + diphenhydramine + diazepam / lorazepam
    used along with to supplement its anti-emetic aid
  - Dexamethasone also used to ↑ its efficacy.
- Gastro Kinetic (read K.D)
- Dyspepsia (G.I disorder)
  also used to stop persistent hiccups.
- GERD

DOMPERIDONE ← Not block by Atropine

- D2 receptor antagonist chemically related haloperidol.
- but pharmacologically related metoclopramide
- less potent and less efficacy
- not crossed to BBB (extrapyramidal side effects rare)
  - but hyperprolactinaemia can occur.
  - Not affect therapeutic effect of Levodopa

Side-effect

- mouth dryness, loose stools
- headache
- galactorrhoea and menstrual cycle.
- cardia arrhythmias (rapid i.v. infusion)

→ USES. (Not for morning sickness)

- anti-emetic for post-operative drug and disease induced.

- CINV is low

CISAPRIDE

→ prokinetic effect
  - due to 5-HT4 agonism
  - weak 5-HT3 antagonism
  → no D_2 receptor blocking

→ accelerate colonic transit (Dom / metoclo not accelerate colonic transit)

→ does not produce EPS or hyperprolactinaemia.

Adverse effect

→ QT prolongation
→ ventricular fibrillation (torsades de pointes)

→ banned in India

MOSAPRIDE (similar to cisapride)

→ No clinically useful anti-emetic action

→ side effects:
  GI disturbances
  CNS disturbances
  insomnia

→ uses:
- non-ulcer dyspepsia
- diabetic gastroparesis
- GERD
- chronic constipation.

→ CYP3A4 inhibitors increase concentrations
↓
macrolide, azole, antidepressants, HIV protease inhibitors.

~~ETORPIDE~~ ITOPRIDE (Japan)

- prokinetic effect due to D_2 antagonism and anti-cholinesterase
- low affinity for 5-HT_4
- Drug interactions like ~~cisa~~ cisa and mosa is less (metabolized by flavin monoxygenases)
- side effects :- CNS and g·I disturbances
  NO · EPS
  galactorrhoea and gynaecomastia

Mainly used for Dyspepsia treatment

CINITAPRIDE

- prokinetic effect :- block 5-HT_2 and D_2
  stimulate 5-HT_4
- uses :- Non-ulcer dyspepsia
  delayed gastric emptying
  GERD
- SIDE effects :- CNS and g·I disturbances
  No QT prolongation

LEVOSULPIRIDE

- act by blocks central as well peripheral D_2 receptors.
- Atypical antipsychotic, prokinetic and anti-emetic

uses :- similar to cinitapride.

5-HT_3 antagonists

ONDANSETRON (prototype)

- Antiemetic drugs for control cancer chemotherapy radiotherapy

highly effective in ⇒ PONV and disease / drug associated

M.O.A

Anticancer drugs / radiotherapy
↓
Tissue damage (in the gut)
↓
release of serotonin (5-HT) from ENT cells
↓
Stimulates extrinsic PAN through 5-HT_3 receptors
↓
impulses to CTZ and STN
↓
induces vomiting.

5HT3 antagonists block

- Apomorphine induce vomiting and motion sickness is not suppressed.
- Not block dopamine receptors
- minor 5-HT_4 antagonists

Ondansetron not used alone alway used in combination ondansetron + dexamethasone ⊕, ondan + promethazine/diazepam

ondansetron + dexamethasone + NK1 enhances efficacy

→ Adminstered befored surgery first choice of drug.

USES.

- CINV
- PONV
- Overdosage used to treat G·I disorders, uraemia and neurological injuries
- Not used for morning sickness
- used in pregnancy only case of hyperemesis gravidarum.

SIDE effects and drug interactions very less.

↓

→ CNS and g·I disturbances (mild)

GRANISETRON

- 10 times more potent than ondansteron in term of efficacy.
- minor 5-HT4 blockage not seen

PALANOSETRON

→ longest acting and highest affinity for 5-HT3 receptors.

→ efficacy similar in acute phase of CINV but more effective in b/w 2 to 5th days.

- US-FDA only this drug in this class for CINV.

Side-effects

→ CNS and g·I disturbances

→ QT prolongation when given with antibiotics and antidepressants

→ i.v injection cause blurring of vision.

RAMOSETRON (developed in Japan)

- used for irritable bowel syndrome.

NK_1 receptor antagonists

↓

in CTZ and NTS → stimulated by substance P.

→ Aprepitant and fosaprepitant

↓

Prodrug given parenterally

APREPITANT

- less effect on 5HT3 D_2 and other receptors also.
- GI motility not affected.
- Oral aprepitant (125 + 80 + 80 mg for 3 days)
  + i.v ondansetron
  + dexamethasone
  ↓
  ↑ anti emetic efficacy > 90% patients
  ↓
  against high emetogenic cisplatin based chemotherapy
- also used for PONV
- Not given in use of QT-prolongation
- weakness, fatigue, flatulence reported.

ADJUVANT ANTI-EMETICS

CORTICOSTEROIDS

- dexamethasone used in combination with ondansetron/metoclopramide
- CINV → acute and delayed
- due to anti-inflammatory property

BENZODIAZEPINES

- Lorazepam / Diazepam used along with metoclopramide or ondansetron.
  ↓
  relieving psychogenic component
  anticipatory vomiting
  amnesia
- also suppress dystonic side effects of metoclopramide.

CANNABINOIDS (Δ^9 tetrahydrocannabinol)

CB_1 receptors in CTZ receptors ~~b~~ supress by this

- Obtained from marijuana (cannabis indica)

DRONABINOL ← synthetic

- used for moderately ~~ent~~ emetogenic chemotherapy.

side effects

- sedation
- central sympathomimetic effects
- hallucinations
- drug dependence