ANTIEMETICS

- Vomiting (emesis) – protective mechanism which serves to eliminate harmful substances from stomach
- It is forceful expulsion of gastric contents to exterior via oral cavity
- It is the means by which upper G.I.T rids itself of its contents when upper G.I.T is distended, irritated
- Vomiting is preceded by nausea – urge to vomit
- Central regulation of vomiting

CTZ

Vomiting centre

CTZ- Relay area of afferent impulses arising from G.I.T, vestibular nuclei

- Outside the BBB
- Rich in D_2, $5HT_3$ ®s
  M_1 H_1 ®s
- Sensory station- incapable of initiating vomiting
- Send signals to vomiting centre

Vomiting centre

- Rich in muscarinic, $5HT_3$ ®s H_1 ®s
- Receives impulses from
  - CTZ
  - NTS
  - Vestibular nuclei
  - Higher centers in brain

NTS-receives impulses from G.I.T → vomiting centre .

Vagal and splanchnic afferents in GIT mucosa are rich in $5HT_3$ receptors

Irritation of G.I.T mucosa – Release of 5HT from ECL cells – stimulation to $5HT_3$ ®s NTS – Vomiting centre

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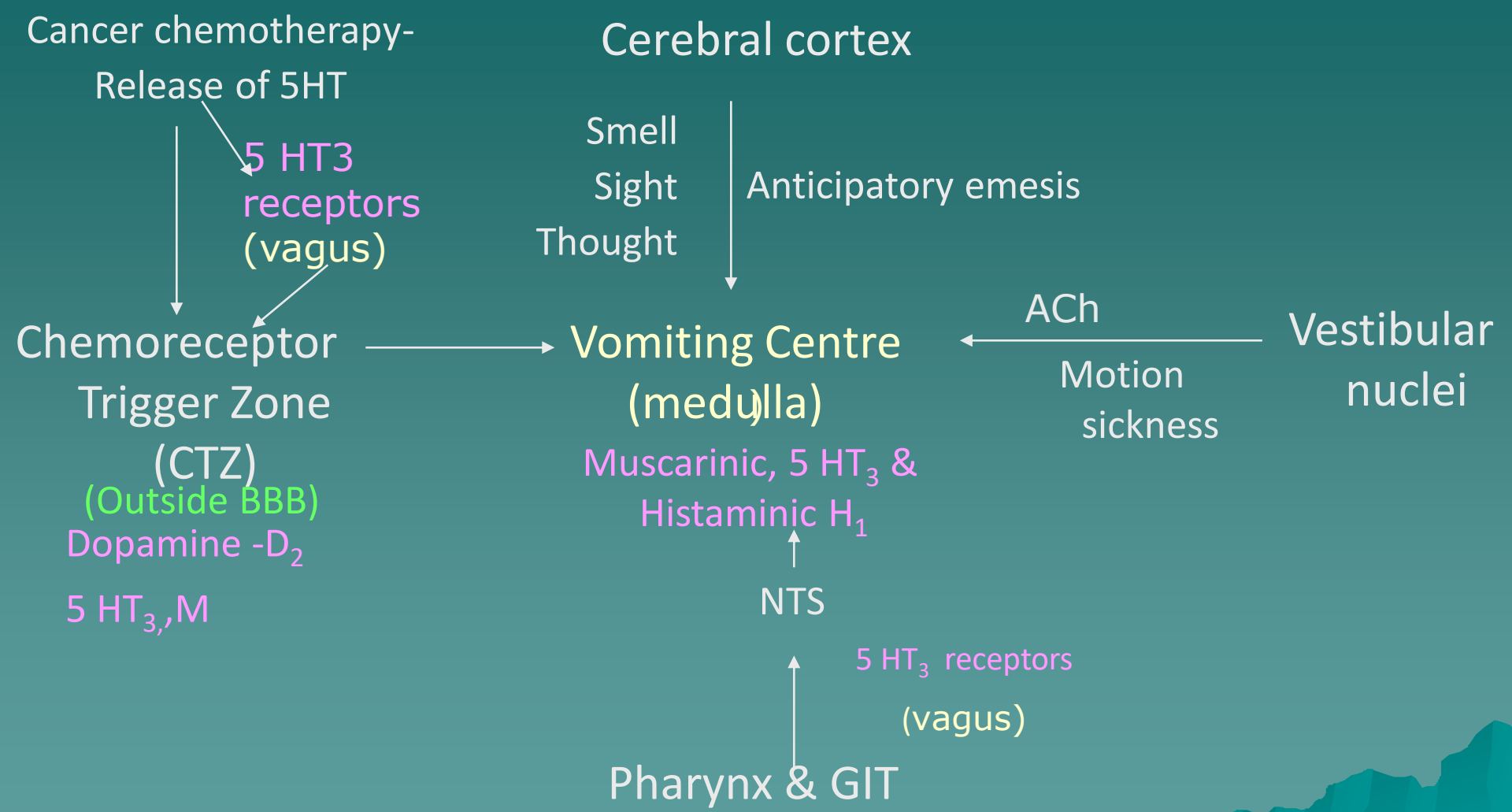
Causes of vomiting

- Morning sickness
- Motion sickness, ototoxic drugs
- Vestibular dysfunction – Vertigo, Meniere dis
- Radiation
- Cancer chemotherapy induced, other drugs
- Post – operative
- GIT disorders → Non-infective
  Infective

Pathophysiology of Emesis



Prokinetics

- Drugs which enhance coordinated activity among the various segments of the GIT to propel the luminal contents

1] Stimulate GIT motility

2] Increase lower esophageal sphinctor tone

3] Speed up gastric emptying

4] Stimulate small intestine motility

5] Enhance colonic transit

Myenteric plexus –control of motor activity

ACh –neurotransmitter of myenteric motor neurons

Mucosal stimulation-release of serotonin-act on $5HT_3$ & $5HT_4$ r. present on interneurons which synapse with cholinergic neurons.

$5HT_4$ ® stimulation-release of Ach

$5HT_3$ ® stimulation-Inhibition of Ach through NO

Dopamine inhibits Ach release

Classification of antiemetics

1. Anticholinergics -
- Scopalamine (Hyoscine)

2. Antihistaminics –
- Promethazine
- Cyclizine
- Meclizine
- Dimenhydrinate
- Cinnarizine
- Doxylamine

3. Antidopaminergics – (D_2 blockade)
- Metoclopramide
- Domperidone
- Phenothiazines

- Chlorpromazine
- Prochlorperazine

4. Antiserotonergic ($5HT_3$ blockade)

- Ondansetron
- Granisetron

5. Adjuvant drugs –

- Glucocorticoids
- benzodiazepines

6. Neurokinin - receptor antagonist

- Aprepitant
- Fosaprepitant

7. Cannabinoid ® - agonist

- Dronabinol
- Nabilone

Anticholinergic

Scopolamine (Hyoscine)

Mechanism of action

- **It blocks muscarinic receptors in CTZ**

Use

Only in Motion sickness

Oral

Intramuscular – 0.2.0.4 mg

- **short duration of action**

Transdermal patch – 1.5 mg – applied behind the pinna

S/E:- Sedation

Dryness of mouth

Less with transdermal patch.

Antihistaminics

Mechanism of action

- **Block H_1, M receptors in CTZ**
- **Sedation.**

A) Promethazine theoclate (Avomin)

Motion sickness

25 mg tablet

B) Cyclizine. Meclizine

Less sedation

Motion sickness

Morning sickness

C) Cinnarizine (Stugeron)

Antivertigo

- Blocks H_1 ® +, inhibits entry of ca^{++} from endolymph into vestibular apparatus

D) Doxylamine – Safest – Morning sickness

Antidopaminergics

Pheothiaziness

A) Chlorpromazine

Mech. Of action – Blocks D_2 receptors in CTZ

Additional – anticholinergic

antihistaminic

Use as antiemetic limited:-

- **Extrapyramidal side effects**
- **Sedation**

Uses

Vomiting not responding to metoclopramide

Vomiting d/t cancer chemotherapy

B) Prochlorperazine (stemetil)

Labyrinthine suppressant

Antivertigo

S/E- extrapyramidal side effects.

Metoclopramide

Mechanism of action

1) Blocks dopaminergic receptors – D_2 in CTZ

2) At high dose blocks $5HT_3$ receptors in CTZ

3) Prokinetic :-

- Enhances upper gastrointestinal

(gastro duodenal) motility and speeds up gastric emptying

- Increases tone of lower gastro-esophageal sphincter, enhance gastric emptying, duodenal peristalsis

a) Enhances release of Ach – ($5HT_4R$) which acts on muscarinic receptors present on smooth muscles of G.I.T.

b) Dopamine inhibits gastrointestinal motolity. Metoclopramide inhibits its action.

- **Pharmacokinetics**

  Oral, parenteral

  Crosses BBB , placenta

  Breast milk +

Side – effects

1) **Extrapyramidal side effects**
2) **Galactorrhoea. Gynaecomastia**

Uses

1) Treatment of vomiting d/t any cause

Not in – Morning

Motion Sickness

Oral- 10 mg tab. Syrup 5 mg /5ml

Inj – 10 mg/ 2 ml

2) As a gastrokinetic

a) Gastro esophageal reflux disease

b) Dyspepsia

c) Emergency GA has to be given, pt has consumed food.

Domperidone

Mechanism of action Same as Metoclopramide

Prokinetic only through D_2 ® antagonism

Advantage over metoclopramide

No extrapyramidal side effects as it doesn't cross BBB

Not available as parenteral preparation- Cardiac arrhythmias.

Prepn – 10 mg tab, syrup – 1mg /ml.

Ondansetron, Granisetron

Mechanism of action

Central action – Blocks 5 HT_3 receptors in CTZ

Peripheral action-

Cytotoxic drugs

↓

Cellular damage

↓

Release of 5 HT

↓

Acts on $5HT_3$ ® present on vagal afferents

↓

Stimulation of CTZ

Advantages

No extrapyramidal side effects

Uses

1. 1st drug of choice in prevention and treatment of vomiting d/t cancer chemotherapy
   - 8 mg i.v before cancer chemotherapy
   - 8 mg – 2 doses
   - oral – 8 mg
2. Radiation sickness vomiting
3. Post –operative vomiting

NK_1 receptor antagonist

Sub.P acts on NK_1 receptor on vagal afferents CTZ

Cisplatin induced delayed phase of vomiting

Cannabinoid receptor agonist

Stimulate CB_1 receptor on neurons around vomiting centre

S/E- Disorientation, Hallucinations

Adjuvant drugs

Glucocorticoids

Dexamethasone

- Enhances action of other antiemetics
- Used during cancer chemotherapy

Benzodiazepines

Lorazepam – 1,2 mg tab, inj- 2 mg/ml

Alprazaolam

Sedative, anxiolytic, amnesia

Pyridoxine

Morning sickness

Prokinetic agents

Cisapride

- Facilitates motility of entire G.I.T
- agonist at $5HT_4$ ®
- Enhances release of Ach

Uses

1. Gastro – esophageal reflux disease
2. Constipation

Tab- 10 mg

S/E –QT interval prolonged- Not used

Mosapride , Tegaserod