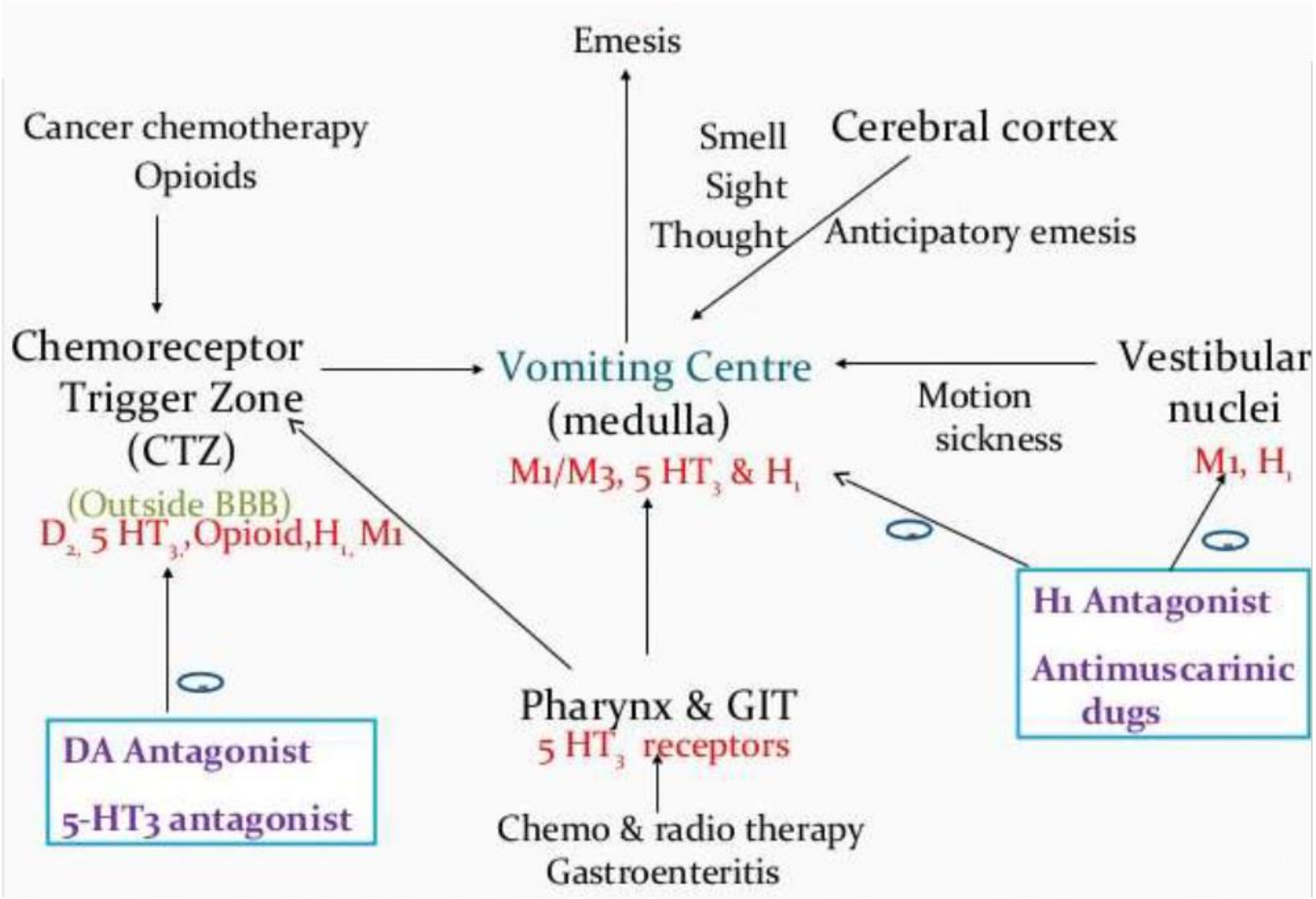
Anti-emetic Drugs

Pharmaceutical Chemistry IV

PHA 482

Pathophysiology of Emesis



- **ACT OF EMESIS:** To get rid the stomach and intestine toxic substances and prevent further ingestion.
- **VOMITING:** Expulsion of gastric contents through mouth due to mass antiperistalsis.
- **NAUSEA:** Uneasy feeling of vomiting.
- **RETCHING:** Series of weaker and unproductive vomiting movements.

Vomiting is a complex process that consists of :

- **PRE-EJECTION PHASE:**

Gastric relaxation and retro peristalsis.

- **RETCHING:**

Rhythmic action of respiratory muscles preceding vomiting and consist of abdominal & intercoastal muscles and diaphragm against a closed glottis.

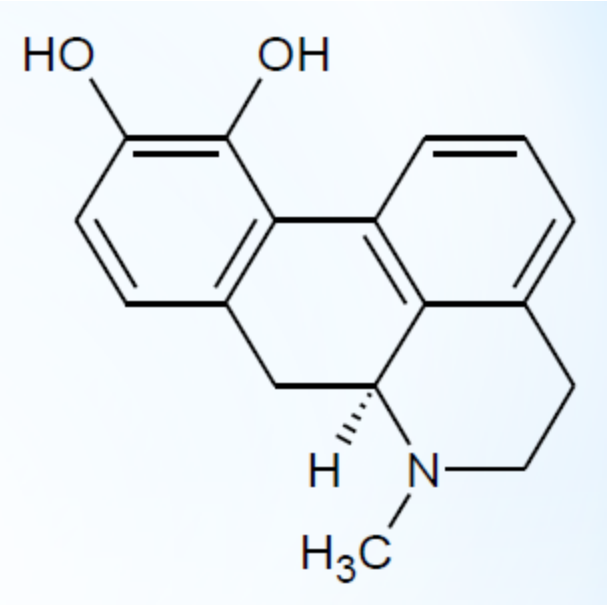
- **EJECTION:**

Intense contraction of abdominal muscles and relaxation of upper oesophageal sphincter.

- Followed by multiple autonomic phenomena:

  Salivation, Shivering, Vasomotor changes

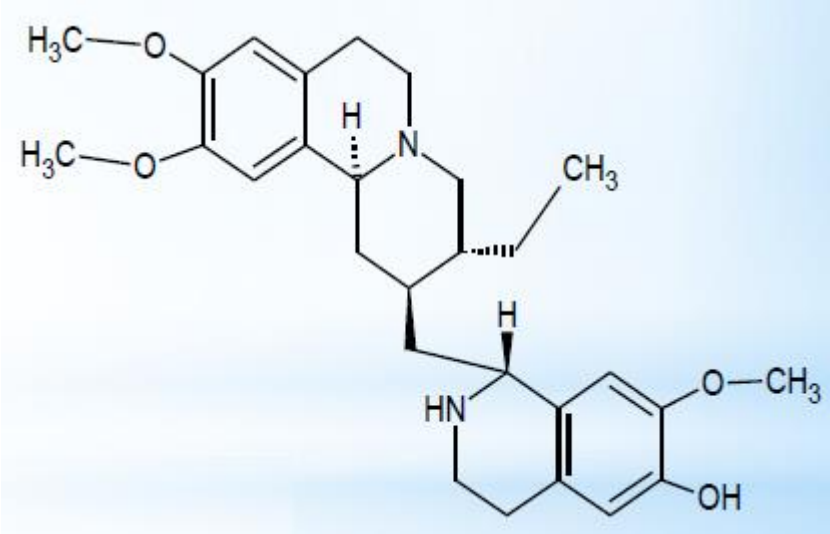
APOMORPHINE



(MOA): Acts centrally by stimulating the medullary CTZ connected with vomiting centre

- Uses: As emetic.

CEPHAELINE



MOA: Locally by irritating the gastric mucosa & centrally by stimulating the medullary CTZ to induce vomiting.

- Uses – as emetic.
- Chemically it is an alkaloid found in ipecac.

EMETICS

- Emetics ⟶ drugs used to evoke vomiting.
- Vomiting ⟶ undesirable substances are ingested.
- At emergency powdered mustard suspension or strong salt solution may be used.

CLASSIFICATION.

- Act on Chemoreceptor Trigger Zone(CTZ).

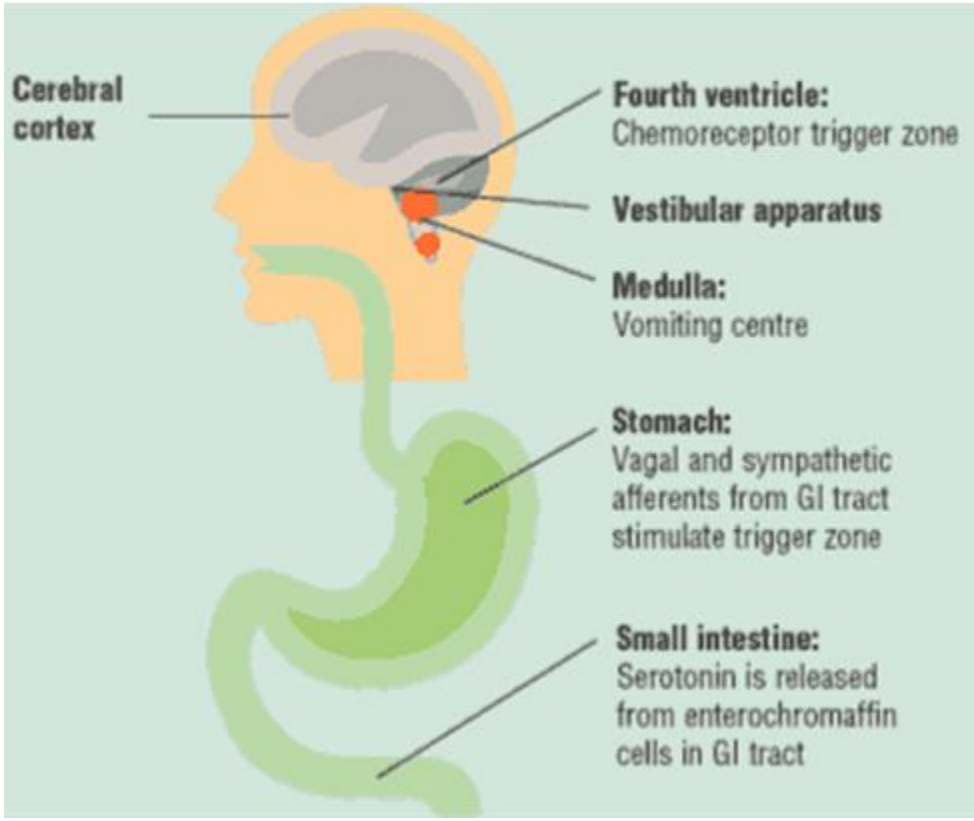
  eg: Apomorphine.

- Act reflexly and on CTZ.

  eg: Cephaeline.

Anti-emetic mechanism

- Anti-emesis process iscoordinated by a central emesis center in **lateral reticular formation of midbrain adjacent** to both **chemoreceptor trigger zone (CTZ) in the area postrema (AP) at the bottom of 4th ventricle and solitary tract nucleus (STN).**
- Lack of **blood-brain barrier (BBB) allows CTZ to monitor** the blood and CSF for toxic substances and to relay information to emesis center to trigger **nausea and vomiting.**



Anti-emetic mechanism

- **Vestibular apparatus generates impulses during motion sickness which**

reach vomiting center via cerebellum. Vestibular apparatus is rich in M1, H1receptors.

- **Emesis also receives information from gut through vagus nerve (via STN)** and **splanchnic afferent nerves via spinal cord. They are rich in 5HT3** receptors.
- **Irritants of GIT mucosa (irritants, chemotherapeutic drugs, radiation,** endogenous toxins and poisons) --- release mucosal serotonin from entero-chromaffin like cells (ECL cells) which activate 5HT3 receptors.
- Inputs to emesis center also come from **cerebral cortex (particularly in** anticipatory nausea & vomiting.
- M1, H1,5HT3 and neurokinin-1 (NK1) receptors are present in **vomiting center.**

CLASSIFICATION OF ANTI-EMETIC DRUGS

- **$5HT_3$ ANTAGONISTS:**

  Ondansetron, Granisetron, Dolansetron, Palonosetron, Ramosetron, Tropisetron.

- **CENTRALLY ACTING DOPAMINE RECEPTOR ANTAGONIST:**

  Metoclopramide, Domperidone, Chlorpromazine, Prochlorperazine

- **HISTAMINE (H1) RECEPTOR ANTAGONIST:**

  Cyclizine, Promethazine, Diphenhydramine, Hydroxyzine

- **ANTICHOLINERGIC (MUSCARINIC RECEPTOR ANTAGONIST):**

  Hyoscine (Scopolamine)

- **NEUROKININE RECEPTOR ANTAGONIST:**

  Aprepitant

- **CANABINOID RECEPTOR AGONIST:**

  Dronabinol, Nabilone

OTHER ANTI-EMETIC DRUGS

- CORTICOSTEROIDS:

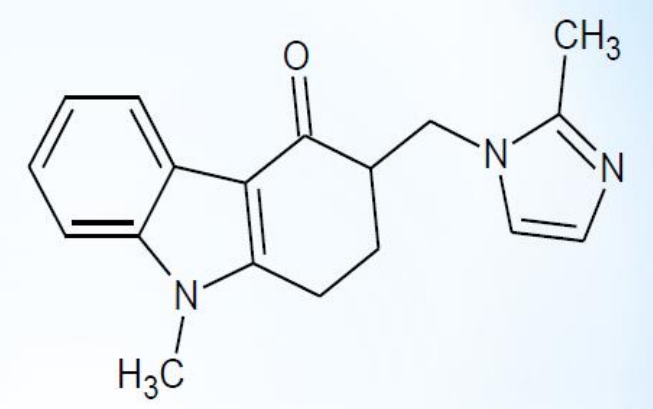
  Betamethasone, Dexamethasone

- VITAMIN B6 (PYRIDOXINE):

- PHOSPHATED CARBOHYDRATE SOLUTION:

$5HT_3$ ANTAGONISTS:

ONDANSETRON



9-methyl-3-[(2-methylimidazol-1-yl)methyl]-2,3-dihydro-1*H*-carbazol-4-one

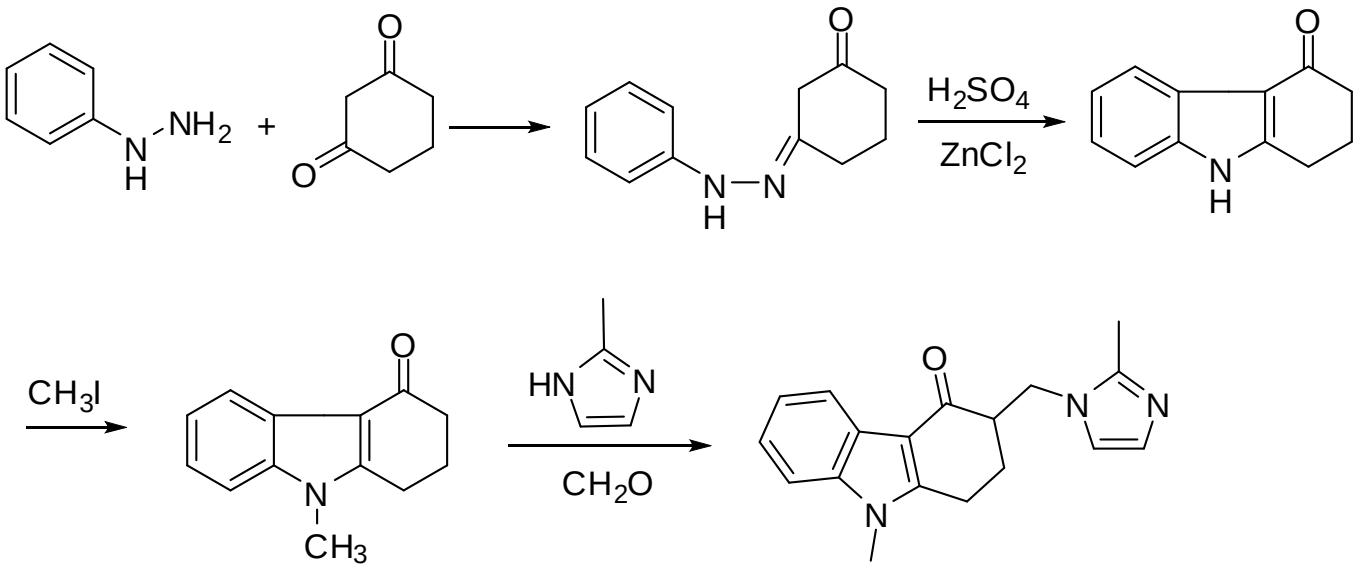
MOA; 5-HT is released from enterochromaffin cells (ECL) of small intestine in response to chemotherapy agents. These stimulate vagal afferents initiating vomiting reflex. Antagonism of 5HT-3 receptors suppress nausea & vomiting

- Anti-emetic effect persists for long time even after they disappear from circulation.

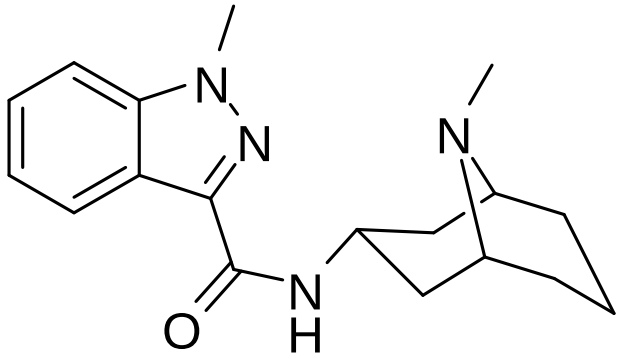
Use: Chemotherapy induced emesis

Side Effects: Constipation/Diarrhoea, Headache, Lightheadness

Synthesis of Ondansetron



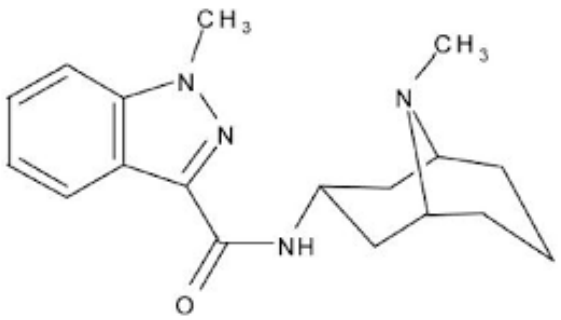
GRANISETRON



1-methyl-N-(9-methyl-9-azabicyclo[3.3.1]nonan-3-yl)-1H-indazole-3-carboxamide

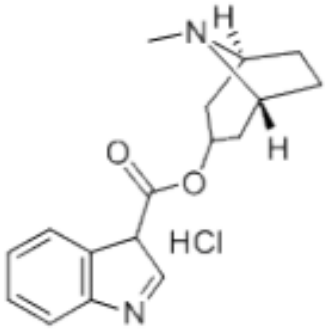
- Has long half life compared to ondansetron

- Chemotherapy induced nausea
- Nausea secondary to upper abdominal irradiation
- Hyperemesis of pregnancy



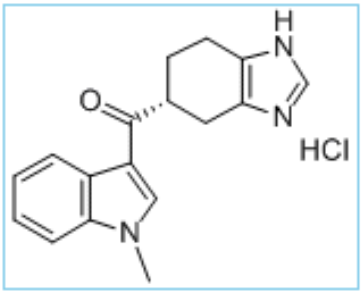
Granisetron

Emetril, Granexa, Granitron,Gratryl, Kytril, Neoset, Setron, Sinarex, Tigron



Tropisetron

Navoban



Ramosetron

Nozia (India)

Iribo(Japan)

Side effect for all: Constipation/ Diarrhoea, Headache

CENTRALLY ACTING DOPAMINE RECEPTOR ANTAGONISTS

METOCLOPRAMIDE:

- Acts centrally blocking D2 receptors in CTZ.
- Used in nausea and vomiting due to GI disorders, in postoperative period and vomiting due to cytotoxic drugs and radiotherapy.

DOMPERIDONE:

- Blocks D2 receptors in CTZ and acts as antiemetic.
- Advantage: doesn't cross BBB – rare extrapyramidal effects
- SE: headache, dryness of mouth, diarrhoea, rashes

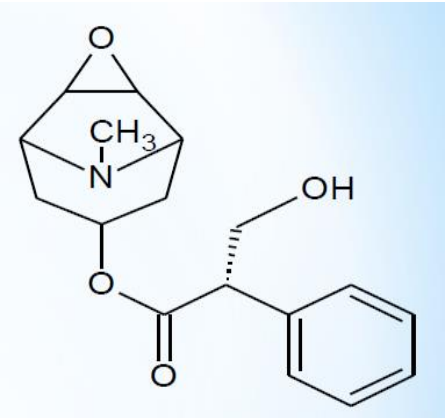
ANTIHISTAMINICS

MOA:

- Act by both relaxing the smooth muscles and also act centrally to depress vomiting centers.
- They diminish vestibular stimulation & depress labyrinthine function.
- H_1 antagonism

ANTICHOLINERGIC (MUSCARINIC RECEPTOR ANTAGONIST):

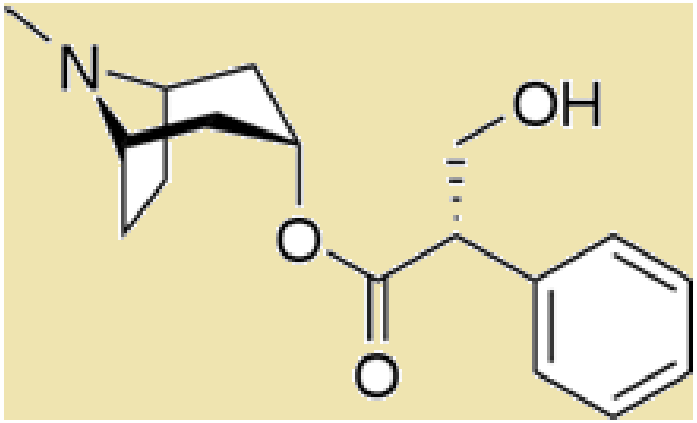
HYOSCINE
(Scopolamine)



9-methyl-3-oxa-9-azatricyclo[3.3.1.$0^{2,4}$]non-7-yl (2*S*)-3-hydroxy-2-phenyl propanoate

- MOA: Blocks conduction of nerve impulses across a cholinergic link in the pathway leading from the vestibular apparatus to the vomiting centre.
- Uses: For motion sickness.

HYOSCYAMINE



[(1*R*,5*S*)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl] (2*S*)-3-hydroxy-2-phenylpropanoate

- L-Hyoscyamine, the active optical isomer of atropine (dl-hyoscyamine), is a tertiary amine anticholinergic gastrointestinal agent.