Pharmacology

Antiemetic

- *Emesis Vomiting occurs due to stimulation of* the *emetic (vomiting) centre situated in the medulla* oblongata.
- Multiple pathways can elicit vomiting.
- **EMETICS**
  - These are drugs used to evoke vomiting.
  - 1. *Act on CTZ : Apomorphine*
  - 2. *Act reflexly and on CTZ : Ipecacuanha*
    - Vomiting needs to be induced only when an undesirable substance (poison) has been ingested. Powdered mustard suspension or strong salts solution may be used in emergency. They act reflexly by irritating the stomach.
  - **Apomorphine**
    - It is a semisynthetic derivative of morphine; acts as a dopaminergic agonist on the CTZ. Injected i.m./s.c. in a dose of 6 mg, it promptly (within 5 min) induces vomiting.
    - It should not be used if respiration is depressed, because it has inherent respiratory and CNS depressant actions.
    - Oral use of apomorphine is not recommended because the emetic dose is larger, slow to act and rather inconsistent in action.
    - Apomorphine has a therapeutic effect in parkinsonism, but is not used due to side effects.
  - **Ipecacuanha**
    - The dried root of Cephaelis ipecacuanha contains emetine and is used as *syrup ipecac (15–30 ml in* adults, 10–15 ml in children, 5 ml in infants) for inducing vomiting.
    - It is less dependable than parenteral apomorphine and takes 15 min or more for the effect, but is safer; has been used as a household remedy.
    - It acts by irritating gastric mucosa as well as through CTZ.

- *All emetics are contraindicated in:*
  - (a) Corrosive (acid, alkali) poisoning: risk of perforation and further injury to esophageal mucosa.
  - (b) CNS stimulant drug poisoning: convulsions may be precipitated.
  - (c) Kerosine (petroleum) poisoning: chances of aspiration of the liquid (due to low viscosity) and chemical pneumonia are high.
  - (d) Unconscious patient: may aspirate the vomitus, because laryngeal reflex is likely to be impaired.
  - (e) Morphine or phenothiazine poisoning: emetics may fail to act.

- **ANTIEMETICS**
  - These are drugs used to prevent or suppress vomiting.
- CLASSIFICATION
  - 1. *Anticholinergics - Hyoscine, Dicyclomine*
  - 2. *H1 antihistaminics*
    - *Promethazine,* Diphenhydramine, Dimenhydrinate, Doxylamine, Meclozine (Meclizine), Cinnarizine.
  - 3. *Neuroleptics Chlorpromazine,*
    - *(D2 blockers) Triflupromazine,* Prochlorperazine, Haloperidol, etc
  - 4. *Prokinetic drugs*
    - *Metoclopramide,* Domperidone, Cisapride, Mosapride, Itopride
  - 5. *5-HT3 antagonists*
    - *Ondansetron,* Granisetron, Palonosetron, Ramosetron
  - 6. *NK1 receptor antagonists*
    - *Aprepitant , Fosaprepitant*
  - 7. *Adjuvant*
    - *Dexamethasone, antiemetics Benzodiazepines,* Dronabinol, Nabilone

- ANTICHOLINERGICS
  - *Hyoscine (0.2–0.4 mg oral, i.m.)*
    - *It is the most* effective drug for motion sickness. However, it has a brief duration of action; produces sedation, dry mouth and other anticholinergic side effects; suitable only for short brisk journies.
    - Antiemetic action is exerted probably by blocking conduction of nerve impulses across a cholinergic link in the pathway leading from the vestibular apparatus to the vomiting centre and has poor efficacy in vomiting of other etiologies.
  - *Dicyclomine (10–20 mg oral)*
    - *It has been used* for prophylaxis of motion sickness and for morning sickness.
    - It has been cleared of teratogenic potential.

- H1 ANTIHISTAMINICS (*See Ch. 11*)
  - Some antihistaminics are antiemetic.
  - They are useful mainly in motion sickness and to a lesser extent in morning sickness, postoperative and some other forms of vomiting.
  - Their antiemetic effect appears to be based on anticholinergic, antihistaminic, weak antidopaminergic and sedative properties.
  - ***Promethazine, diphenhydramine, dimenhydrinate***
    - These drugs afford protection of motion sickness for 4–6 hours, but produce sedation and dryness of mouth. By their central anticholinergic action they block the extrapyramidal side effects of metoclopramide while supplementing its antiemetic action
  - ***Promethazine theoclate*** *(AVOMINE 25 mg tab.)*
    - This salt of promethazine has been specially promoted as an antiemetic, but the action does not appear to be significantly different from promethazine HCl.
  - ***Doxylamine***
    - *It is a sedative H1 antihistaminic* with prominent anticholinergic activity. Marketed in combination with pyridoxine Oral absorption of doxylamine is slow, and its t½ is 10 hr.
    - The side effects are drowsiness, dry mouth, vertigo and abdominal upset.
    - *Dose: 10–20 mg at bed time; if needed additional doses* may be given in morning and afternoon.
    - TM- DOXINATE, GRAVIDOX, VOMNEX, NOSIC 10 mg with pyridoxine 10 mg tab.
  - ***Meclozine (meclizine)***
    - *It is less sedative and* longer-acting; protects against sea sickness for nearly 24 hours.
    - TM- DILIGAN: meclozine 12.5 mg + nicotinic acid 50 mg tab;
    - PREGNIDOXIN: meclozine 25 mg + caffeine 20 mg tab.
  - ***Cinnarizine***
  - *It is an antivertigo drug having* antimotion sickness property. It probably acts by inhibiting influx of Ca^{++} from endolymph into the vestibular sensory cells which mediates labyrinthine reflexes.

- NEUROLEPTICS
  - The older neuroleptics (phenothiazines, haloperidol) are potent antiemetics; act by blocking D2 receptors in the CTZ; antagonize apomorphine induced vomiting and have additional antimuscarinic as well as H1 antihistaminic property. They have broad spectrum antiemetic action effective in:
    - (a) Drug induced and postoperative nausea and vomiting (PONV).
    - (b) Disease induced vomiting: gastroenteritis, uraemia, liver disease, migraine, etc.
    - (c) Malignancy associated and cancer chemotherapy (mildly emetogenic) induced vomiting.
    - (d) Radiation sickness vomiting (less effective).
    - (e) Morning sickness: should not be used except in hyperemesis gravidarum.
  - Neuroleptics are less effective in motion sickness.
  - ***Prochlorperazine***
    - *This D2 blocking phenothiazine* is a labyrinthine suppressant, has selective antivertigo and antiemetic actions.
    - It is highly effective when given by injection in vertigo associated vomiting, and to some extent in CINV.
    - Prochlorperazine is used as an antiemetic, but not as antipsychotic
    - *Dose: 5–10 mg BD/TDS oral, 12.5–25 mg by deep i.m.* injection.
    - TM- STEMETIL 5 mg tabs., 12.5 mg/ml inj, 1 ml amp, VOMTIL 5 mg tab.

- PROKINETIC DRUGS
  - These are drugs which promote gastrointestinal transit and speed gastric emptying by enhancing coordinated propulsive motility.
  - This excludes traditional cholinomimetics and anti-ChEs which produce tonic and largely uncoordinated contraction.
  - **Metoclopramide**
    - Metoclopramide, a substituted benzamide, is chemically related to procainamide, but has no pharmacological similarity with it. it is a commonly used antiemetic.
    - **Actions**
      - *GIT: Metoclopramide has more prominent effect* on upper g.i.t.; increases gastric peristalsis while relaxing the pylorus and the first part of duodenum → speeds gastric emptying, especially if it was slow. through both dopaminergic and serotonergic receptors
      - *Dose: 10 mg (children 0.2–0.5 mg/kg) TDS oral or i.m. For* CINV 0.3–2 mg/kg slow i.v./i.m.
      - TM- PERINORM, MAXERON, REGLAN, SIGMET, 10 mg tab; 5 mg/5 ml syr; 10 mg/2 ml inj.; 50 mg/10 ml inj.

- **Domperidone**
  - It is a D2 receptor antagonist, chemically related to haloperidol, but pharmacologically related to metoclopramide. The antiemetic and prokinetic actions have a lower ceiling.
  - *Dose: 10–40 mg (Children 0.3–0.6 mg/kg) TDS.*
  - TM- DOMSTAL, DOMPERON, NORMETIC 10 mg tab, 1 mg/ ml susp, MOTINORM 10 mg tab, 10 mg/ml drops.
- **Cisapride**
  - This benzamide derivative is a prokinetic with little antiemetic property, because it lacks D2 receptor antagonism.
  - Effects of cisapride on gastric motility resemble metoclopramide, i.e. gastric emptying is accelerated, LES tone is improved and esophageal peristalsis is augmented
- **Mosapride**
  - A subsequently introduced congener of cisapride with similar gastrokinetic and LES tonic action due to 5-HT4 agonistic (major) and 5-HT3 antagonistic (minor) action in the myenteric plexus.
  - *Dose: 5 mg (elderly 2.5 mg) TDS.*
  - TM- KINETIX 5 mg tab, MOZA, MOZASEF, MOPRIDE 2.5 mg, 5 mg tabs; MOZA MPS: 5 mg + methylpolysiloxane 125 mg tab.
- **Itopride**
  - Another substituted benzamide produced It has D2 antidopaminergic and anti-ChE (ACh potentiating) activity, but very low affinity for 5-HT4 receptor.
  - *Dose: 50 mg TDS before meals.*
  - TM- GANATON, ITOFLUX, ITOKINE, ITOPRID 50 mg tab.

5-HT3 ANTAGONISTS

Ondansetron

- It is the prototype of a distinct class of antiemetic drugs developed to control cancer chemotherapy/radiotherapy induced vomiting, and later found to be highly effective in PONV and disease/drug associated vomiting as well.
- *Pharmacokinetics: Oral bioavailability of ondansetron* is 60–70% due to first pass metabolism It is eliminated in urine and faeces, mostly as metabolites; t½ is 3–5 hrs, and duration of action is 8–12 hrs (longer at higher doses).
- TM- EMESET,VOMIZ, OSETRON, EMSETRON 4,8 mg tabs, 2 mg/ml inj in 2 ml and 4 ml amps. ONDY, EMESET 2 mg/5 ml syrup.

Granisetron

- It is 10 times more potent than ondansetron and probably more effective during the repeat cycle of chemotherapy
- *Dose: 1–3 mg diluted in 20–50 ml saline and infused i.v. over* 5 min before chemotherapy, repeated after 12 hr.
- TM- GRANICIP, GRANISET 1 mg, 2 mg tabs; 1 mg/ml inj. (1, 3 ml amps).

Palonosetron

- It is longest acting 5-HT3 blocker having the highest affinity for the 5-HT3, receptor.
- *Dose: 250 µg by slow i.v. injection 30 min before* chemotherapy. Do not repeat before 7 days. For PONV 75 µg i.v. as a single injection just before induction.
- PALONOX 0.25 mg/ml inj, PALZEN 0.25 mg/50 ml inj.

- NK1 RECEPTOR ANTAGONISTS
  - Realizing that activation of neurokinin (NK1) receptor in CTZ and NTS by substance P released due to emetogenic chemotherapy and other stimuli plays a role in the causation of vomiting, selective antagonists of this receptor have been produced, and are being used as antiemetic.
  - **Aprepitant**
    - It is a recently introduced selective, high affinity NK1 receptor antagonist that blocks the emetic action of substance P, with little effect on 5 HT3 and D2 or other receptors.
    - Gastrointestinal motility is not affected.
    - *Dose: For CINV—125 mg before chemotherapy + 80 mg each* on 2nd and 3rd day (all oral) along with i.v. ondansetron + dexamethasone.
    - For PONV—40 mg (single dose) oral before abdominal or other surgery.
    - TM- APRECAP, APRESET, APRELIFE, EMPOV 125 mg (one cap) + 80 mg (2 caps) kit.

- ADJUVANT ANTIEMETICS
  - **Corticosteroids (e.g. dexamethasone 8–20 mg i.v.)**
    - It can partly alleviate nausea and vomiting due to moderately emetogenic chemotherapy, but are more often employed to augment the efficacy of other primary antiemetic drugs like metoclopramide and ondansetron against highly emetogenic regimens.
    - Corticosteroids benefit both acute and delayed emesis.
    - The basis of the effect appears to be their anti-inflammatory action. They also serve to reduce certain side effects of the primary antiemetic.
  - **Benzodiazepines**
    - The weak antiemetic property of BZDs is primarily based on the sedative action. Used as adjuvant to metoclopramide/ondansetron, diazepam/lorazepam (oral/ i.v.) help by relieving the psychogenic component, anticipatory vomiting and produce amnesia for the unpleasant procedure.
    - They also suppress dystonic side effects of metoclopramide.
  - **Cannabinoids Δ9 Tetrahydrocannabinol (Δ9 THC)**
    - It is the active principle of the hallucinogen *Cannabis indica that* possesses antiemetic activity against moderately emetogenic chemotherapy.
    - It probably acts through the CB1 subtype of cannabinoid receptors located on neurones in the CTZ and/ or the vomiting centre itself.
  - **Dronabinol**
    - *It is pure Δ9THC produced synthetically or* extracted from *Cannabis.*
    - *In a dose of 5–10 mg/m2 BSA* orally (repeated as required) it can be used as an alternative antiemetic for moderately emetogenic chemotherapy in patients who cannot tolerate other antiemetics or are unresponsive to them

To be continued……