Drugs acting on GIT

Treatment of vomiting, diarrhoea and constipation

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Emesis (Vomiting)

- **Emesis:** is the **expulsion** of the contents of the stomach up through the mouth
- **Nausea** is the feeling that **precedes emesis**
- **Vomiting** reflex may work to **eliminate toxic** substances that have been ingested.
- **Nausea and vomiting** may be **side effects of cytotoxic drugs & radiation** for cancer

Mechanisms of nausea & vomiting

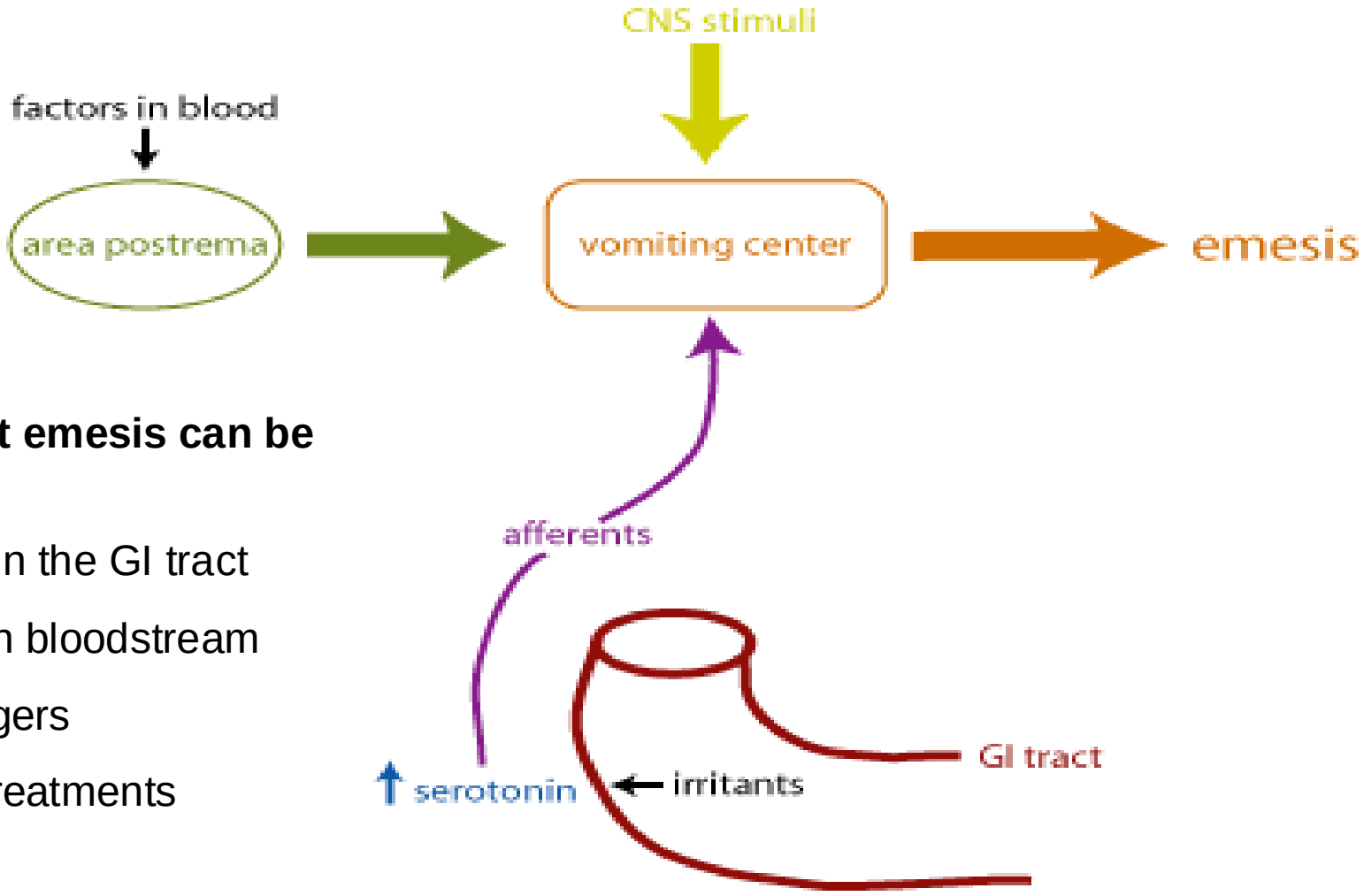
There are 2 sites that play a major role in the vomiting reflex:

- **Vomiting centre** present in the **reticular** formation of the **medulla** & is **stimulated** by stimuli from:
  - Chemoreceptor trigger zone (CTZ; rich with D2 receptors)
  - Vestibular system of the ear (rich with H1 & muscarinic receptors)
  - Afferent vagal fibers (rich with 5HT**3** receptors) from periphery (GIT, CVS, GUS)
  - The cerebral cortex (e.g. smell, sight, emotion)

Mechanisms of nausea & vomiting

- **CTZ** located outside the BBB in the area **postrema** on the floor of the **4th ventricle**
- It is stimulated directly by drugs & chemical stimuli present in **blood** or **CSF**
- It responds to **chemical** stimuli (as **drugs**, toxins, uraemia, radiation) through activation of **dopamine** or **serotonin** receptors.

Emesis



Ways that emesis can be triggered

- Irritation in the GI tract
- Factors in bloodstream
- CNS triggers
- Cancer treatments

Anti-emetics

- Drugs **prevent or treat** nausea & vomiting
- **Choice** of anti-emetic drugs depends on the **aetiology** of the vomiting; therefore:
- Identify the cause
- Treat the underlying cause as:
  - Diabetic ketacidosis, menigitis, digoxin or antiepileptic toxicity

Major Anti-emetic Drugs

- Anti-muscarinics
- Antihistamines
- Phenothiazines (anti-psychotics)
- Metoclopramide
- Domperidone
- Ondansetron
- Others (Benzodiazepines & Dexamethasone)

Anti-muscarinc agents

Hyoscine (scopolamine)

- **Prevention & treatment of motion sickness**
- Mechanism:
  - **Central**: blocks M-receptors in vomiting centre
  - **Peripherally** on the GIT

Antihistamines

- 1st Generation antihistamines
  - **Diphenhydramine**, **cyclizine,** **Chlopheniramine**

- **Prevention of motion sickness** by:
  - Blockade of **H_1** and **M-receptors** in the vomiting centre
  - **Sedative** effect
- Usually these are not drugs of first choice in other emesis

Phenothiazines

- Are **anti-psychotic agents** with **potent** anti-emetic effect
- Their action by:
  - **Blocking D_2** receptors in **CTZ**
  - **Anti-muscarinc** & **antihistaminic** actions
- Indicated in **disease- & drug-induced vomiting**
- May produce **extrapyramidal effects** by blocking D_2 receptors in basal ganglia

- They also have antimuscarinic effects

Phenothiazines examples

- **Prochlorperazine** (stemetil)
- **Promethazine (**Phenergan**)**

- Others:
  - Chlorpromazine (largactil)
    - Have limited uses (adverse effects)

Metoclopramide (Plasil)

- **Effective** anti-emetic
- **Superior** to phenothiazines in emesis of gastroduodenal, hepatic & biliary disease
- Has **central & peripheral** actions:
  - Blocks **D_2 receptors** in CTZ
  - Peripheral: **enhances** action of **Ach** at muscarinic nerve endings in the **gut**

Therapeutic uses of metoclopramide

- N&V associated with GIT diseases
- With cytotoxic drugs
- With radiotherapy
- In migraine
- Prokinetic agent to increase peristalsis & gastric emptying

Adverse effects of metoclopramide

- **Acute dystonia** reactions:
  - Torticollis, facial spasm, trismus, oculogyric crisis
- **Diarrhoea**

Domperidone

- **Selectively block D_2** receptors in the CTZ (like the phenothiazines)
- Has **no** acetylcholine-like effects (unlike metoclopramide)
- Relief of N &V of:
  - **GIT disorders**
  - **Cytotoxics** & **other drug** therapy

Domperidone

- Is **less** likely to cause **central** effects (less sedation & dystonias) than metoclopramide & the phenothiazines because it does **not** readily **cross BBB**.
- Prolonged therapy may produce **gynecomastia & galactorrhoea**

$5HT_3$ antagonists: Ondansetron

- **Selective blocker of $5HT_3$-receptors**:
  - **Central in CTZ & peripheral in gut**
- Effective for prevention of:
  - **Cytotoxic-induced** N & V
  - **Radiotherapy-induced** N & V

Note: Cytotoxics release 5HT from entero-chromaffin cells in gut mucosa activating $5HT_3$ receptors in gut & CNS causing N&V

Ondansetron

- May be given by **IV** injection or **infusion** immediately **before cytotoxic** therapy
- Followed by **oral** administration for up to **5 days**

- Adverse effects:
  - **Constipation**, headache & **flushing**

Other Anti-emetics

- **Benzodiazepines**: **Lorazepam**
  - Often used to control N&V **before** the start of **cytotoxic** chemotherapy producing useful transient amnesia

- **Corticosteroids: Dexamethasone**
  - Anti-emetic effect by **blocking PG synthesis**

Therapy of some forms of Vomiting

Motion sickness & vestibular disorders:

- Drugs of choice:
  - **Hyoscine**
  - **Diphenhydramine**
  - Cinnarizine
  - Cyclizine

Meniere's disease:

- **Cinnarizine**
- **Betahistine**
  - Improve blood flow to the inner ear

Acute attack of Meniere's disease:

- **Cyclizine or prochlorperazine** may be given rectally or by intramuscular injection.

Drug-induced vomiting:

- **Prochlorperazine or metoclopramide**.
- Oipioid-induced N&V respond to **cyclizine**

Anti-diarrhoeal drugs

Diarrhoea

- Refers to **frequent or liquid bowel** movements
- **Acute, chronic**
- May be mild **without complications**
- But in **infants & children** it is severe can cause **dehydration** quickly
- Diarrhoea results from an **imbalance** between **secretion & reabsorption of fluid & electrolytes**
- **Two** major **factors** in diarrhea are:
  - **Increased motility** of the GI tract
  - **Decreased absorption of fluid**

Causes of Diarrhoea

- **Infections** with enteric organisms:
  - Bacteria, viruses
  - Protozoa as amoebiasis & giardiasis
- **Food poisoning & traveler's** diarrhoea
- **Inflammatory bowel disease:**
  - Crohn's disease
  - Ulcerative colitis
- **Drugs:** antibiotics (Antibiotic-associated colitis)
- **Malabsorption**

- Examples of **serious diarrhoeal** diseases e.g. dysentery, cholera

Treatment of diarrhoea

- **Eliminating** the underlying **cause e.g. by specific antimicrobial** agent
- **Giving fluids and electrolyte** replacement
  - **Oral rehydration therapy**
- **Antidiarrhoeal drugs** provide symptomatic relief:
  - **Antispasmodics**
  - **Antimotility drugs**
  - **Adsorbants & Bulk forming agents**

Oral rehydration therapy (ORT)

- The **1st line** of treatment is **prevention** or treatment of **fluid** and **electrolyte depletion** particularly **in acute diarrhoea of children**
- Treat majority of **acute gastroenteritis (GE) of children (virus)**
- Important in **infants** and **elderly** patients
- **Is simple, effective, cheap & easy** to use

Oral rehydration preparations

- Replacement of fluid & electrolytes lost through diarrhoea can be achieved by giving **solutions** containing: Na, glucose, K, etc…
- For **acute diarrhoea**
- Intestinal absorption of **Na & water** is **enhanced by glucose**

- Suitable ORS should contain an **alkalinizing agent** to **counter acidosis**

Oral rehydration preparations

- Rehydration should be **rapid** over **3** to 4 hours
- Once rehydration is complete further dehydration is prevented by **encouraging** patients to **drink fluids**
- In infants **breast-feeding** should be **offered** between oral rehydration drinks
- **Severe** dehydration: **IV fluids & electrolytes**

Symptomatic Antidiarrhoeal Drugs

- These drugs **increase** intestinal content to control **acute diarrhoea:**
  - **Increase viscosity**
  - **Prolong transit time**

- Two types of **drugs** often used in combination:
  - **Opioids**
  - **Anti-muscarinics**

- These are used for **short-term** symptomatic **relief** of **acute** diarrhoea in **adults**
- **not** recommended:
  - For acute diarrhoea in **children** (under 2 years old), because of risk of respiratory depression
  - In **infective** diarrhoea
- **Caution** in ulcerative **colitis**
- These agents **delay** passage of intestinal **content** leading to:
  - increase water absorption
  - increase intestinal content viscosity.
- **Antidiarrhoeal action**

Codeine

- Codeine & other opioids produce constipation by **activation** of **opioid** receptors on **smooth** muscle of the gut **decreasing** forward **peristalsis** & increasing **segmentation**
- Codeine is useful for **non-infective** acute diarrhea in **adults**
- Contraindicated in:
  - **Infective** diarrhoea & **antibiotic-associated colitis** (AAC)
  - **Active inflammatory** bowel disease (as acute UC)

Codeine

- **Adverse effects**:
  - Nausea, sedation
  - **Respiratory depression**
  - **Dependence**

Diphenoxylate

- Its related to pethidine
- has actions on the bowel **similar** to **codeine**
- It is **used** as:
  - **Adjunct** to rehydration in **acute diarrhoea**
  - In **mild ulcerative colitis**
- It is usually mixed with small dose atropine (**lomotil**)
- Its t½ is 3 hours
- **Overdose** may produce **respiratory depression** & manifestations of atropine poisoning.

Loperamide (Imodium)

- structurally similar to diphenoxylate
- Used as:
  - **Adjunct** to **rehydration** in acute diarrhoea in **adults** & **children over 4 years**.
  - In **mild chronic diarrhoea in adults**.
- Its contraindications are similar to the above drugs

Naloxone (opioid antagonist) antagonises actions of **codeine, diphenoxylate & loperamide** when there is overdose **intoxication**

Adsorbent & bulk forming agents

- Adsorbants such as **kaolin, pectin & chalk** are **no** more recommended for acute diarrhoea because of their **low** therapeutic **efficacy**.
- Bulk forming agents such as **ispaghula & methylcellulose** are useful in:
  - **Controlling** faecal **consistency** & **reducing** its fluidity in **ileostomy** & **colostomy**
  - **Controlling diarrhoea** associated with **diverticular disease.**

Specific drug therapy

- **Helicobacter GE: ciprofloxacin**
- **Shigellosis: ciprofloxacin**
- **Typhoid fever: ciprofloxacin, cefotaxime**
- **AAC: metronidazole, vancomycin**
- **Amoebiasis: metroniodazole**
- **Giardiasis: metronidazole**
- **Octreotide** (a somatostatin analogue): diarrhoea of **carcinoid**

Laxative agents

Constipation

- Is the passages of **hard stool less frequently** than the patient's own normal pattern.
- **Prevention** of constipation since childhood is important.
- Preventing constipation:
  - Regular **defecation**
  - Use of **balanced diet** containing adequate **fluid** intake and high **fibre** intake (vegetables, fruits and cereals)
- **Low fibre** diet has an important **aetiological** role in development of constipation, haemorrhoids and diverticulitis.

Therapeutic indications of la

- **Lower GIT procedures** as surgery, radiology and endoscopy
- **Anal lessions** like anal fissure and haemorrhoids
- **Mega colon** (Hirschprung disease) in children
- **Drug-induced** constipation (like opioid-induced)
- **Hepatic encephalopathy**
- **After antihelminthics** to encourage expulsion of worms to the outside

Routes of administration of laxa

- Ussually **orally**
- Occasionally **rectally** (suppositories or rectal enema)

Dangers of abuse of laxative

Regular or **excessive** or **chronic use** of laxative should be **avoided** because may produce the following risk:

- **Dependence and atonic** non-functioning colon
- **Water and electrolyte change** (hypokalaemia, hyponatraemia)
- **Steatorrhoea** (malabsorption of fat)
- **Hypocalcaemia and osteomalacia**

Contraindication of laxative

- **Undiagnosed abdominal pain**
- **Intestinal obstruction**
- **Inflammatory bowel disease**

Classification of laxatives

- **Bulk-forming laxative**
- **Osmotic laxative**
- **Faecal softeners**
- **Stimulant laxatives**

Bulk-forming laxative

Bulk forming laxative

- Site of Action: **Small and large intestine**
- Onset of Action: **12 - 72 hours**
- Cause the stool to be **bulkier** and to **retain** more **water**, as well as forming an emollient gel, making it easier for peristaltic action to move it along.
- They should be **taken** with plenty of **water**.

Bulk-forming laxative

Bran

- **Is hydrophilic indigestible** vegetable **fibres** obtained from cereals
- Is the **residue** obtained when **flour** is made from **cereals** and consists of the cell wall of cereals
- Wheat bran is **taken** with **food or fruit juice**
- Is the **most effective** bulk-forming preparation
- Bran contain ~**40% fibres** which are not digestible by human enzyme

Bulk-forming laxative

Mechanism of action of bran

Hydrophilic effect → Increase faecal water and mass

↓

Decrease viscosity

↓

Increase faecal transit

↓

Laxative effect

Therapeutic uses of bran

- **Prevention of constipation** in people with small hard stools resulting from low-fibre diet
- **Irritable bowel syndrome** (IBS) and **diverticulosis**
- **Colostomy and ileostomy**
- **Anal lesion** as anal fissure and haemorrhoids

Adverse effects of bran

- **Flatulence**
- **Intestinal obstruction**, may avoid with adequate fluid intake
- **Interference with absorption** may occur like of glucose, calcium and drugs.

Bulk-forming laxative

Methylcellulose

- **Useful** for patients who **cannot tolerate bran**
- It takes water to swell to a colloid about 25 times its original volume resulting in laxative effect

Osmotic laxatives

- These cause the intestines **to hold more water** within, **softening** the stool.
- There are **two** principal types, **saline and hyperosmotic**

Osmotic laxative

Saline Osmotic: Magnesium sulphate (Epsom salt)

- Site of Action: **Small and large intestine**
- Onset of Action: **0.5 - 6 hours**
- Is an inorganic **powerful** osmotic **purgative**
- It **acts within 3 hrs** by its osmotic effects
- It should be **used on empty stomach** and **with fluids**
- **Useful** when **rapid clearing** and **evacuation** of the colon is required as **before**:
  - **Endoscopy**
  - **Surgery**
  - **radiology**

Mg_2SO_4 side effects

- May cause **nausea** and intestinal **colic**
- May alter a patient's **fluid and electrolyte balance.**
- Should be **avoided** in **renal impairment** because of its potent effect and toxicity resulting from absorption of Mg

Osmotic laxative

Hyperosmotic: Lactulose

- Is a synthetic **disaccharide**, which is **not affected** by intestinal **disaccharidase** and so **not absorbed** from GIT
- Site of Action: **Colon**
- Onset of Action: **0.5 - 3 hours**
- works by the osmotic effect, which **retains water** in the **colon**, **lowering the pH** and **increasing** colonic **peristalsis**
- It **discourages** the proliferation of ammonia-producing microorganisms.
- Is **useful** in **hepatic encephalopathy** (portal systemic) to prevent onset of hepatic coma
- May produce **flatulence and colic**

Hyperosmotic: Glycerin

- Used as **suppositories**
- Has a mild **stimulant** action on the **rectum** by the **irritant action**

Stimulant laxatives

- These **increase** intestinal **motility** and often **cause** abdominal **colic**
- **Prolonged used** may cause **atonic non-functioning colon and hypokalaemia**
- Action site: **colon**

Bisacodyl (Dulcolax)

- Produce direct **stimulation** of sensory **nerve** ending in the **colon** from the lumen
- May used orally (action in 6-10hr) or rectally (1hr)
- Useful in:
  - **Constipation**
  - **Before surgery**
  - **Endoscopy**
  - **Radiology of the lower GIT**

Senna

- Is **absorbed** in the **small intestine** and **excreted** into the **colon** where it stimulates **bowel motility**
- Is **widely used**:
  - **Constipation**
  - **Before surgery**
  - **Before endoscopy**