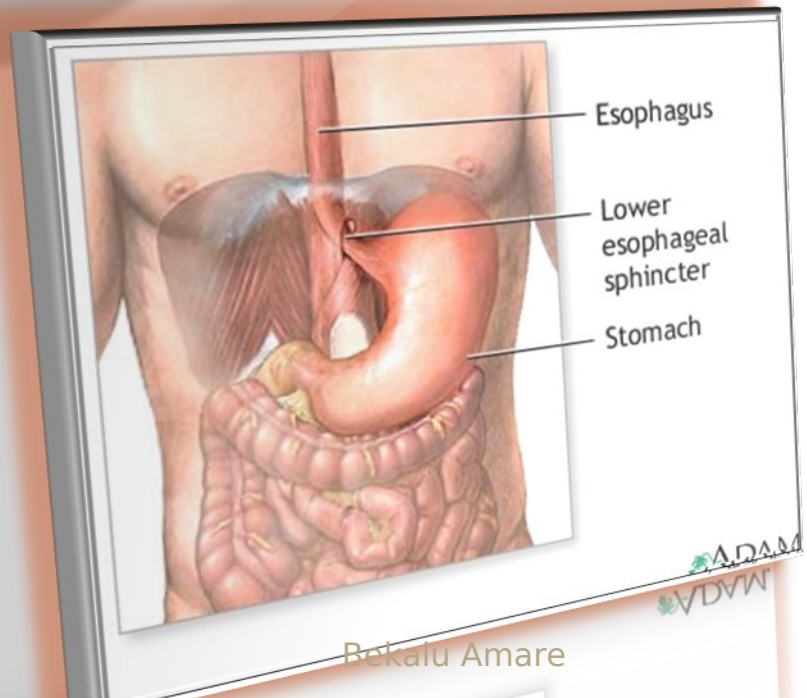


GI Pharmacology





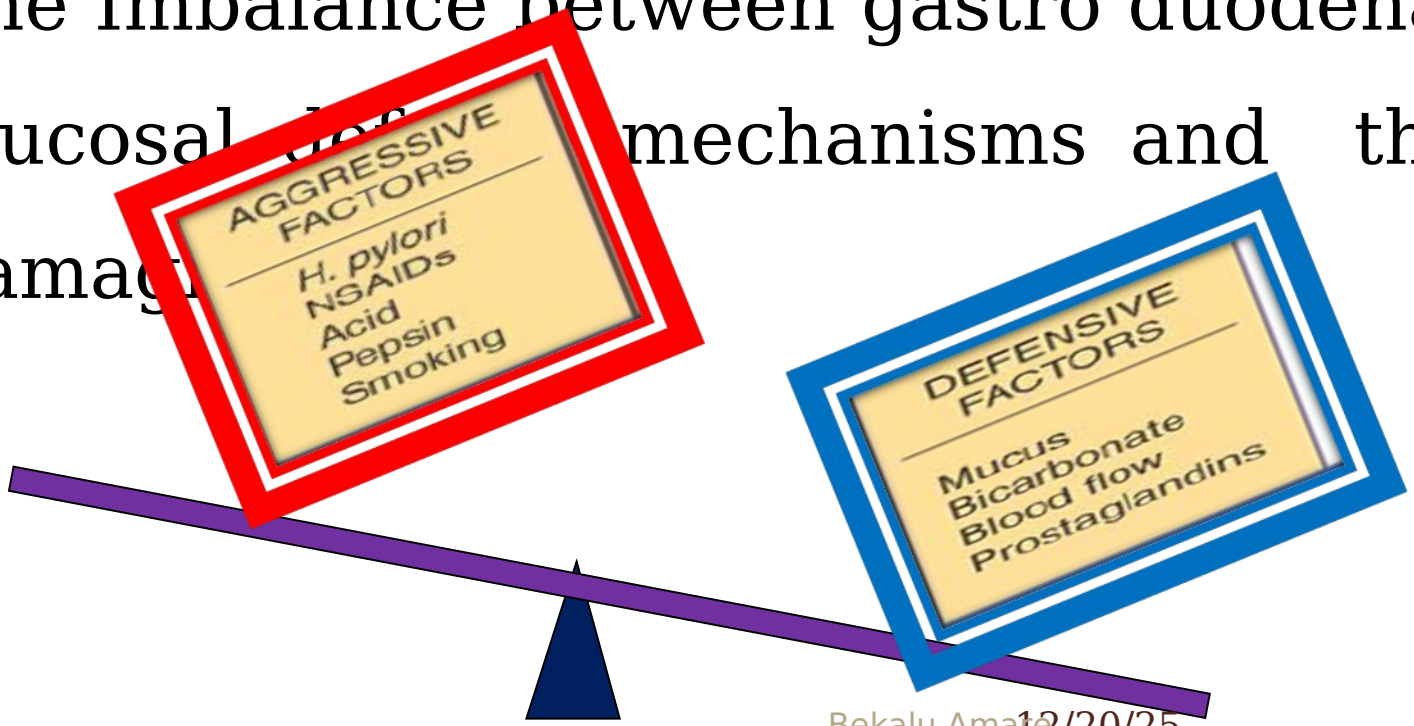


GASTROINTESTINAL DISORDERS

- Acid-peptic disease
  - Peptic ulcer disease (gastric & duodenal)
  - Stress-related mucosal injury
- Constipation & diarrhea
- Nausea & vomiting

Peptic Ulcer Disease (PUD)

- **A burning epigastric pain exacerbated by fasting and improved with meals.**
- The Imbalance between gastro duodenal mucosal def mechanisms and the damag



Types of Ulcer	Mechanisms
H. Pylori associated ulcer	• **It produce virulent factors that damages the mucosa such as: urease enzymes** • **Produced ammonia that enables the organism to survive in the acidic environment of the stomach and may erode the mucus barrier** • **Increase gastric acid secretion** • **Increase pepsinogen 1 & disrupt mucous protective layer**
NSAID induced ulcer	▪ **Direct irritation of the mucosal lining** ▪ **systemic pharmacologic actions: inhibits biosynthesis prostaglandin: affecting mucosal integrity and repair**

Secretion of gastric acid

- Acid (HCl) is secreted from gastric **parietal cells** by a proton pump H+/K+ ATPase

Secretion of HCl by parietals enhanced by 3 major endogenous stimuli (activators of proton pump)

1. **Acetylcholine** stimulates M_3 Ach-Rs - ↑ **Ca^{++}** in parietal cells
2. **Gastrin** activates gastrin Receptor - ↑ **Ca^{++}** in parietal cells
3. Ach and Gastrin activate release of **Histamine** from enterochromaffin-like cells (ECL) which stimulates H_2 Rs on parietal cells (the main pathway of proton pump activation)

Drug therapy for PUD

- ***Anti-secreting agents***

i. **Histamine H_2-receptor antagonists**: ***cimetidine, ranitidine, famotidine, nizatidine***

ii. **Proton pump inhibitors**: ***omeprazole, lansoprazole, pantoprazole, Rabeprazole***

iii. **Muscarinic** antagonists (**Anticholinergics)**: ***pirenzepine*** (M_1 antagonist)

- ***Antacids:*** ***Magnesium hydroxide ,Magnesium trisilicate, Aluminium hydroxide, Sodium bicarbonate, Calcium carbonate***
- ***Mucosal protective agents:*** **Bismuth compounds, Sucralfate and Prostaglandin analogue: misoprostol**
- ***Anti-infective agents(*****Anti-microbial Agents)**

➢ **Metronidazole, TTC, amoxicillin, clarithromycin**

Proton pump inhibitors (PPI)

- **Irreversibly** inhibits the H^+/K^+-ATPase (the proton pump), the terminal step in the acid secretory pathway - potent

Drugs:

- ✓ **Omeprazole (prototype drug)** - **Lansoprazole**
- ✓ **Rabeprazole** - **Esmoprazole (s-isomer of omeprazole)**
- ✓ **Pantoprazole**

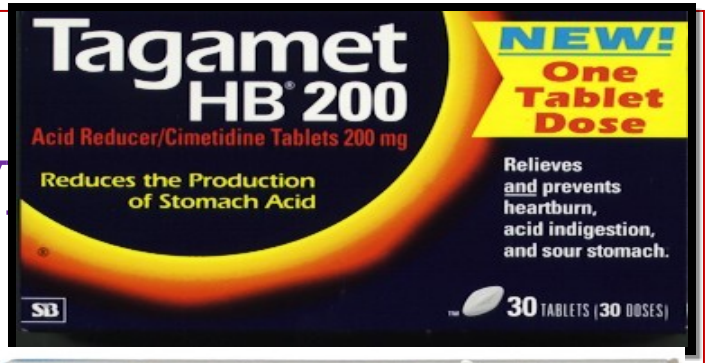
Adverse effects

- ✓ **Nausea, abdominal pain, diarrhea, flatulence**
- ✓ ***Hypergastrinimia*** **(risk of rebound hypersecretion upon discontinuation)**
- ✓ **Deceased acidity may result in infection**

Histamine H_2 receptor blockers

Drugs:

- **Cimetidine (Prototy**
- **Ranitidine**
- **Famotidine**
- **Nizatidine**





- **MOA: Reversible antagonists of H_2-histamine receptors on parietal cells ⇒ block histamine induced stimulation of acid secretion.**

Pharmacodynamics

- Direct stimulation of acid secretion by Ach & gastrin reduced by H_2 receptor blockers
- Effective at **inhibiting nocturnal acid secretion** ⇒ as Histamine is responsible for nocturnal acid secretion(90%)
- **All are equal in Efficacy** but
- Differ in **Potency**, (**F > R/N > C**)

Adverse effects

- Diarrhea, headache, drowsiness, fatigue, muscular pain, and constipation
- **Endocrine effect: Galactorrhea** (due to ↑ed plasma prolactin level) in women;
  - ✓ **Gynecomastia**, impotence, loss of libido, decrease sperm count in males – due to inhibition of binding of **androgen** to its receptor and decreasing **estradiol** metabolism - commonly with larger dose and/or prolonged use of **cimetidine** ; others don't have such effect
  - ✓ **Feminizing effects in men**

Therapeutic uses of PPI and H_2 receptor antagonist

- Treatment of **erosive esophagitis** and active duodenal ulcer and for long-term treatment of pathologic hypersecretory conditions (e.g. **Zollinger-Ellison syndrome**) – **drug of choice**
- Effective in promoting **healing** of duodenal and gastric ulcers; but **recurrence** is common
- **Acute** stress ulcers
- Non ulcerative dyspepsia
- Ulcer caused by NSAIDs
- To treat uncomplicated **GERD**

Muscarinic antagonists

- **Drugs** : **Pirenzepine, Clindinium**
- **MoA**: **inhibit muscarinic receptor on parietal and ECL.**
- **Anticholinergics** with **anxiolytics** can be used to treat stress induced dyspepsia.

  eg. **Librax®** (**clindinium bromide + chlordiapoxide**)

- **Librax®** is **the DOC for stress induced ulcer**

Adverse effects:

- ✓ **Anticholinergic side effects (anorexia, blurry vision, constipation, dry mouth, sedation)**

Antacids



- They are weak bases
- Basic compounds that are used to **neutralize** hyperacidity of the gastric content - neutralization reaction to form water and a salt
- Mainly indicated for **simple dyspepsia and heartburn**
- **Commonly used antacids**: ***Magnesium hydroxide Magnesium trisilicate, Aluminium hydroxide, Sodium bicarbonate, Calciu***



Therapeutic uses of antacids

- **Dyspepsia**
- Symptomatic relief in PUD and GERD
- Adjuncts for healing of PUD

Antacids Drug interaction

Alter gastric pH

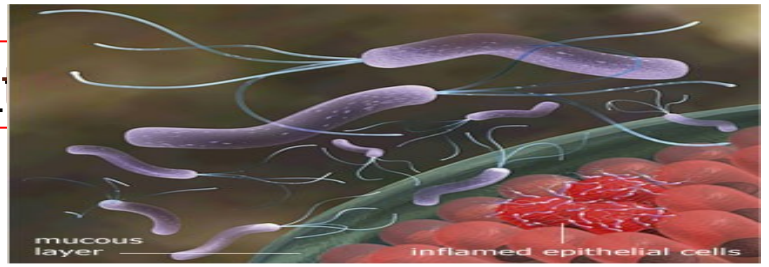
- ↓ Absorption of drugs which needs acidic medium

  e.g. ***ketoconazole, Itraconazole, iron*** etc.

❖ **Chelation with other drugs forming insoluble complex** ⇒ ↓ absorption

e.g. **Tetracycline, fluroquinolones, ketoconazole** and **oral anticoagulant**

H.Pylori Eradica



H. Pylori

- *H. pylori* infection has been implicated as a **causative** factor in the production of PUD, particularly, **duodenal** ulcers, as well as a risk factor for **gastric cancer**
- Multiple drugs have been revaluated in the therapy of H.pylori
  - **No single** agent is effective in eradicating the organism
  - **Combination therapy** for 14 days provides the greatest efficacy

H. pylori Eradication



- ***H. pylori***
- **Combination antibiotic therapy:**
  - ***Bismuth – Disrupts bacterial cell wall***
  - ***Clarithromycin – Inhibits protein synthesis***
  - ***Amoxicillin – Disrupts cell wall***
  - ***Tetracycline – Inhibits protein synthesis***
  - ***Metronidazole – Used often due to bacterial resistance to amoxicillin and tetracycline, or due to intolerance***

1. **PPI Based Triple Therapy**
2. **Bismuth-Based Quadruple Therapy**
3. **Sequential Therapy**

PPI Based Triple Therapy

PPI	**Standard dose**	**BID (QD)**	**10-14 days**
Clarithromycin	**500 mg**	**BID**	**10-14 days**
Amoxicillin	**1 g**	**BID**	**10-14 days**
PPI	**Standard dose**	**BID**	**10-14 days**
Clarithromycin	**500 mg**	**BID**	**10-14 days**
Metronidazole	**500 mg**	**BID**	**10-14 days**

Omeprazole 20 mg BID; Lansoprazole 30 mg BID; Pantoprazole 40 mg BID; Rabeprazole 20 mg BID (QD); Esomeprazole 20 mg BID or 40 mg QD

Bismuth-Based Quadruple Therapy

Bismuth subsalicylate	**525 mg**	**QID**	**10-14 days**
Metronidazole	**250 mg**	**QID**	**10-14 days**
Tetracycline	**500 mg**	**QID**	**10-14 days**
PPI	**Standard dose**	**BID or QD**	**10-14 days**

Omeprazole 20 mg BID; Lansoprazole 30 mg BID; Pantoprazole 40 mg BID; Rabeprazole 20 mg BID (QD); Esomeprazole 20 mg BID or 40 mg QD

Sequential Therapy

PPI	Standard dose	BID	1-5 Days
Amoxicillin	1 g	BID	1-5 Days
Followed by			
PPI	Standard dose	BID	6-10 Days
Clarithromycin	500 mg	BID	6-10 Days
Metronidazole or	500 mg	BID	6-10

Omeprazole 20 mg BID; Lansoprazole 30 mg BID; Pantoprazole 40 mg BID; Rabeprazole 20 mg BID (QD); Esomeprazole 20 mg BID or 40 mg QD

Advantages of Sequential Therapy over Triple Therapy

- ✓ ***Higher eradication rate of the bacteria***
- ✓ ***Lower the antibiotic resistance rate***
- ✓ ***Better patient adherence***
- ✓ ***Lower incidence of side effects associated with treatment***

Drugs used in the treatment of constipation







Constipation

- It is infrequency passage of stool which may be due to decrease in colon motility or difficulty in evacuation.
- Causes
  - In most cases **no specific cause** is found
    - Lack of dietary fiber, drugs, hormonal disturbances, neurogenic disorders & systemic illnesses

Drugs Used in The Treatment of Constipation



1. Bulk forming laxatives →hydrophilic indigestible colloids which form hydrated, bulky and soften mass→ distend the colon→↑peristalsis

Eg. ***Methylcellulose***

2. Stool surfactants →lower the surface tension →easy defecation eg. ***Docusate of Na, K and Ca***

3. Lubricants →makes stool slippery →stool slides easily eg. **Mineral oil (liquid paraffin)**

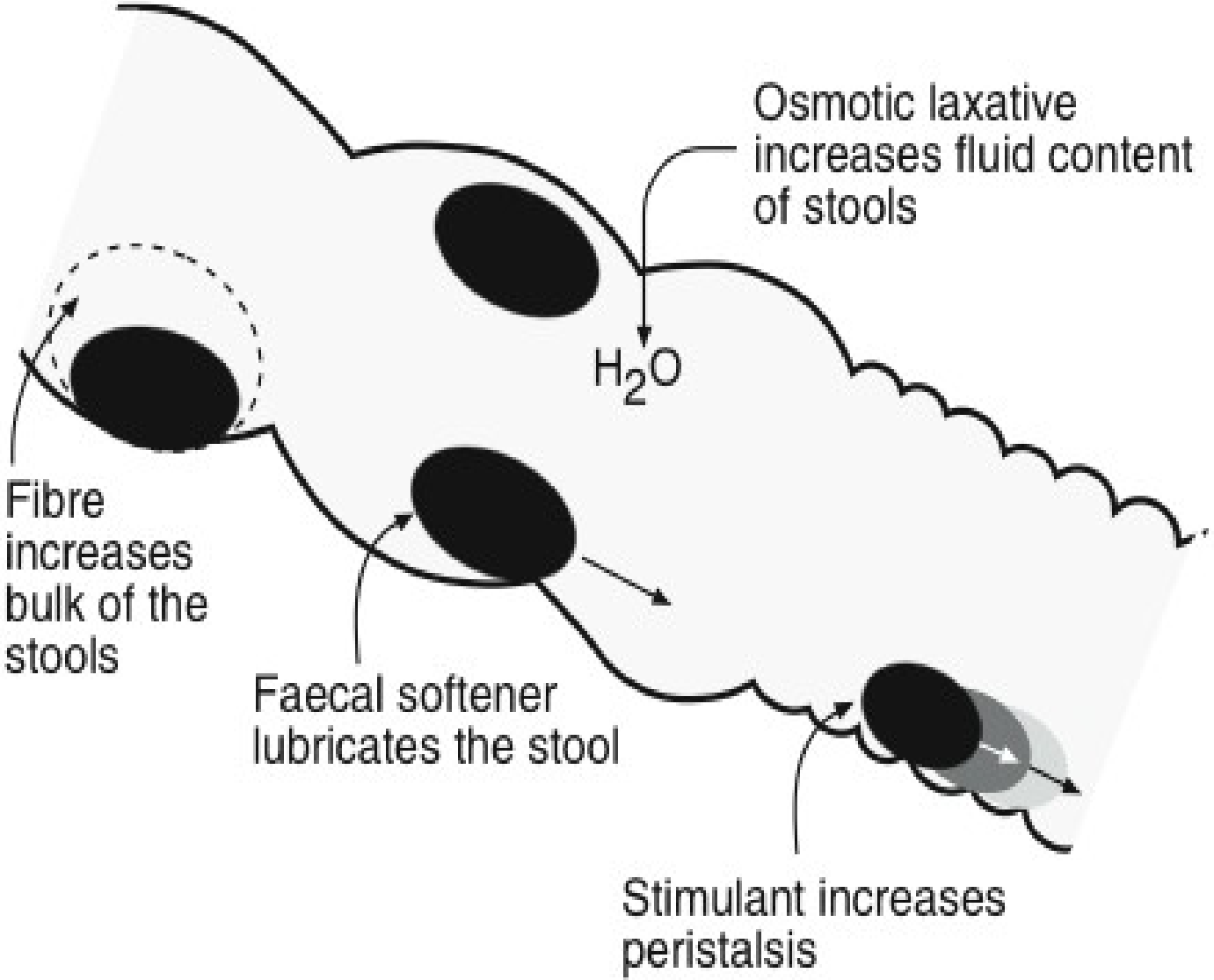
4. Osmotic laxatives →cause the intestine to retain more water →increase stool fluidity

Eg. **mannitol, Lactulose**

5. Stimulant (Irritant) laxatives →induce bowel movement

- Eg. **Castor oil, Bisacodyl, and glycerine**

Drugs used in the treatment of constipation



ANTIDIARRHEAL AGENTS





Diarrhea

- It is " too rapid evacuation of too fluid stools."
- It is roughly defined as greater than 250mg/day stool production containing 70-95% water
  - ✓Excessive secretion of electrolytes & water into the intestinal lumen
  - ✓Exudation of protein & fluid from the mucosa
  - ✓Altered intestinal motility resulting in rapid transit (& $\downarrow_{ed}$ fluid absorption)

Approaches to the treatment of severe acute diarrhea

- ✓ Maintenance of **fluid** and **electrolyte** balance
- ✓ Use of **anti-infective** agents to treat the underlying **cause**
- ✓ Use of **antidiarrheal** agents
  - ***Opioid agonists :*** **Loperamide** is the drug of **first choice** for **traveller's** diarrhea and **Diphenoxylate** is used as alternative.
  - ***Colloidal bismuth compounds:*** **Bismuth subsalicylate:** possess an antisecretory, anti-inflammatory, and antimicrobial effect and are used in the treatment and prevention of traveler's diarrhea
  - ***Bile salt–binding resins:*** **Cholestyramine**

Antiemetics



- Vomiting is regulated centrally by the ***vomiting center*** & the ***chemoreceptor trigger zone*** (*CTZ*)
  - Both of which lie in the **medulla**
- The CTZ is sensitive to chemical stimuli & is the main site of action of many emetic & antiemetic drugs.
- The CTZ also regulates motion sickness (condition caused by conflicting spatial signals arising from the vestibular apparatus & the eye)
- Impulses from the CTZ pass to those areas of the brain stem called vomiting center-that control & integrate the visceral & somatic functions involved in vomiting.

- **Nausea:** Inclination to vomit
- **Vomiting:** The ejection/expulsion of gastric content through the mouth
- **<u>Causes of N and V:</u>**

✓ ***Adverse effects of drugs***

✓ ***Systemic disorder/infection***

✓ ***Pregnancy***

✓ ***Radiation/chemotherapy***

Antiemetic drugs

1. H_1 receptor antagonists:

diphenhydramine, cyclizine, meclizine, promethazine

- **MoA**: **H_1** histamine receptor antagonists
- Are effective in **motion** sickness and vomiting caused by substances that act locally in the **stomach**
- ***Promethazine*** *and* ***doxylamine*** are used in vomiting of pregnancy (**morning** sickness)

2. Anticholinergics

- ***Scopolamine* (hyoscine):** used in the prevention and treatment of **motion sickness**
- Suppresses nerve traffic in neuronal pathway from **vestibular apparatus** of inner ear to vomiting center
- All antimotion sickness drugs act better when taken **30min-1hour** before starting journey

Note: ***The antihistaminic and anticholinergic antiemetics are the First drug of choice for motion sickness***

3. Anti-dopaminergics

Act mainly as antagonists of the dopamine D_2 receptors in the CTZ, in addition they also block histamine and muscarinic receptors

Used for treating nausea and vomiting associated with **cancer**, **radiation** therapy, cytotoxic drugs, opioids, **anesthetics**

A. Phenothiazines: *chlorpromazine*

- **Severe morning sickness of pregnancy**

B. Butyrophenones: haloperidol and droperidol

C. Metoclopramide='Gastric hurrying' agent /prokinetic agents

Therapeutic uses

- Gastro-esophageal reflux disease(GERD)
- Gastric **hypomotility**

Adverse effects

Long term use may cause parkinsonism, galactorrhea and gynecomastia

Serotonin /5-HT_3 receptor antagonists

- ***Ondansetron, granisetron, dolasetron,***
- **MoA**: Potent and selective antagonists of 5-HT_3 **receptor**s, primarily in the **CTZ**; and also on **peripheral** vagal nerve terminals

- Are the **most** widely used drugs for **chemotherapy-induced** emesis; also used to prevent or treat **post-operative** nausea and vomiting