Pharmacology - 2

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Gastrointestinal and Antiemetic Drugs

Pharmacology-2/ Gastrointestinal & Antiemetic Drugs/
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LEARNING OUTCOMES

After the student finishes studying this chapter, he will be able to:

- Classify the drugs used for hyperacidity, such as H_2-receptor antagonists, proton pump inhibitors, antacids, etc., and the drugs used as antiemetic.
- Illustrate the mechanisms of actions of these drugs.
- Numerate the remarkable side effects and drug-drug interactions of these studied medications.
- Clarify the remarkable clinical aspects of these drugs indications.
- Explain the most remarkable points regarding the pharmacokinetic and pharmacodynamic parameters of these drugs.

Drugs Used to Treat Peptic Ulcer Disease and Gastroesophageal Reflux Disease:

❖ The two main causes of peptic ulcer disease are:

- **Infection** with gram-negative *Helicobacter pylori* , also:
- The **use** of nonsteroidal anti-inflammatory drugs (NSAIDs).
- Increased hydrochloric acid (HCl) **secretion**.
- Inadequate **mucosal defense** against gastric acid.

❖ **Treatment approaches include:**

1. Eradicating the *H. pylori* infection.
2. Reducing secretion of gastric acid with the use of **PPIs** or **H2 receptor antagonists**. and/or
3. Providing agents that protect the gastric mucosa from damage, such as misoprostol and sucralfate.

Gastrointestinal and Antiemetic Drugs

ANTIMICROBIAL AGENTS

Amoxicillin GENERIC ONLY
Bismuth compounds PEPTO-BISMOL, KAOPECTATE
Clarithromycin BIAXIN
Metronidazole FLAGYL
Tetracycline GENERIC ONLY

H_2 – HISTAMINE RECEPTOR BLOCKERS

Cimetidine TAGAMET
Famotidine PEPCID
Nizatidine AXID
Ranitidine ZANTAC

PROTON PUMP INHIBITORS

Dexlansoprazole DEXILANT
Esomeprazole NEXIUM
Lansoprazole PREVACID
Omeprazole PRILOSEC
Pantoprazole PROTONIX
Rabeprazole ACIPHEX

PROSTAGLANDINS

Misoprostol CYTOTEC

ANTIMUSCARINIC AGENTS

Dicyclomine BENTYL

ANTACIDS

Aluminum hydroxide GENERIC ONLY
Calcium carbonate TUMS
Magnesium hydroxide MILK OF MAGNESIA
Sodium bicarbonate ALKA-SELTZER

MUCOSAL PROTECTIVE AGENTS

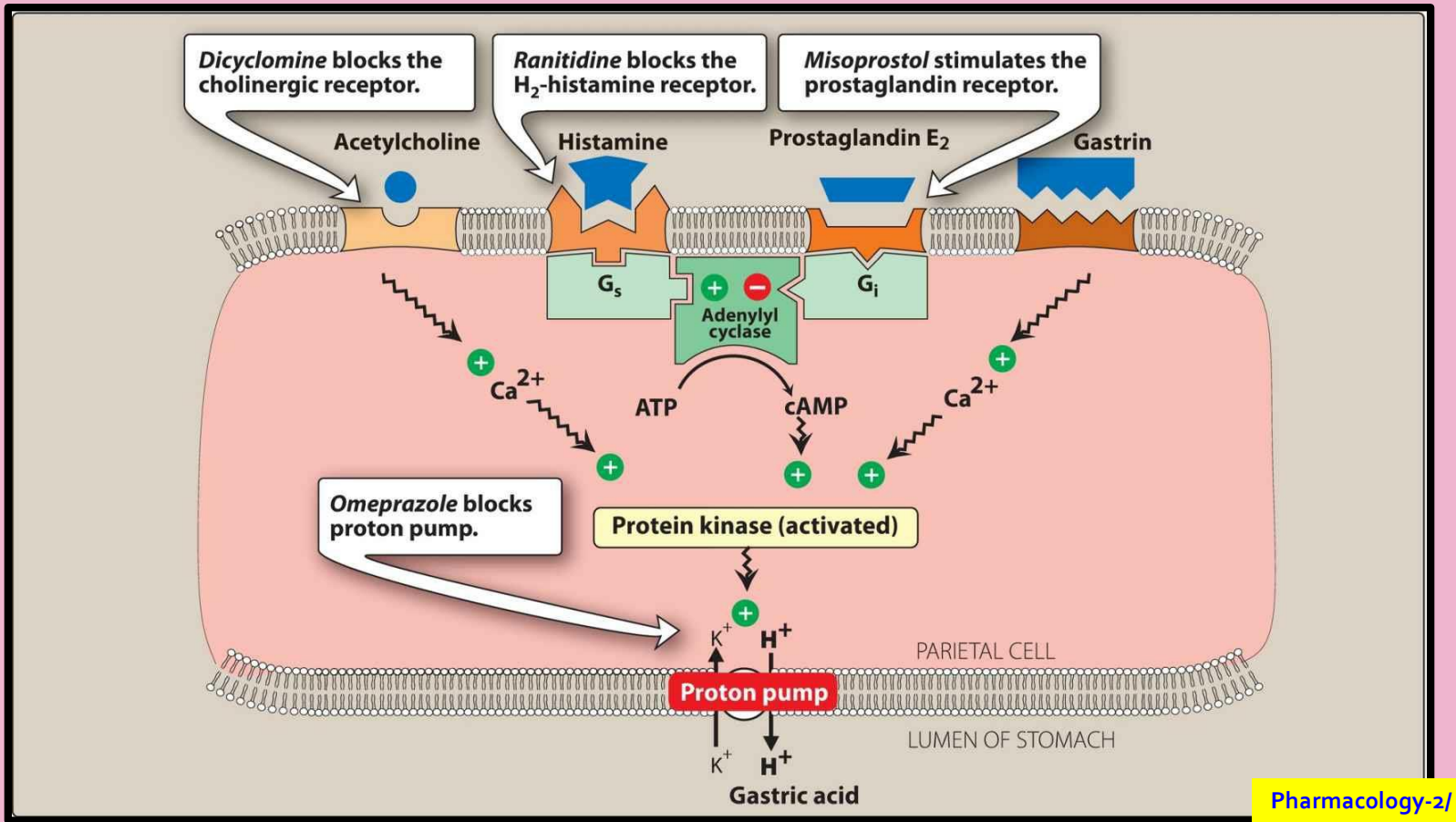
Bismuth subsalicylate PEPTO-BISMOL
Sucralfate CARAFATE

AGENTS THAT REDUCE INTRAGASTRIC ACIDITY:

PHYSIOLOGY OF ACID SECRETION:

Cholecytokinin- B receptors

- The parietal cell contains receptors for gastrin (CCK-B), histamine (H_2), and acetylcholine (muscarinic, M_3).



Antimicrobial agents:

- Patients with peptic ulcer disease (duodenal or gastric ulcers) who are infected with *H. pylori* require antimicrobial treatment.
- Eradication of *H. pylori* with various combinations of antimicrobial drugs results in rapid healing of active ulcers and low recurrence rates (less than 15%, compared with 60% to 100% per year for ulcers healed with acid-reducing therapy alone).
- Currently, **quadruple therapy** of bismuth subsalicylate, metronidazole, and tetracycline plus a PPI is a recommended first-line option.
- **Bismuth subsalicylate:** an **antacid** medication used to treat temporary discomforts of the stomach and gastrointestinal tract, such as diarrhea, indigestion, heartburn and nausea {90% eradication rate}.

- **Triple therapy:** consists of a PPI combined with amoxicillin (metronidazole may be used in penicillin-allergic patients) plus clarithromycin is a preferred treatment when rates of clarithromycin resistance are low and the patient has no prior exposure to macrolide antibiotics.

H2 receptor antagonists:

- Gastric acid secretion is stimulated by acetylcholine, histamine, and gastrin.
- The receptor-mediated binding of acetylcholine, histamine, or gastrin results in the activation of protein kinases, which in turn stimulates the H+/K+-adenosine triphosphatase (ATPase) proton pump to secrete hydrogen ions in exchange for K+ into the lumen of the stomach.

- By competitively blocking the binding of histamine to H_2 receptors, these agents reduce the secretion of gastric acid.
- The four drugs used in the US {cimetidine, famotidine, nizatidine, and ranitidine} inhibit basal, food-stimulated, and nocturnal secretion of gastric acid, reducing acid secretion by approximately 70%.
- Cimetidine was the first H_2 receptor antagonist.
- However, its utility is limited by its adverse effect profile and drug–drug interactions.
- They are reversible competitive inhibitors of H_2 receptors.
- Their use has decreased with the advent (rising) of PPIs.

- All four agents are equally effective in promoting the healing of duodenal and gastric ulcers.
- Recurrence is common if ***H. pylori*** is present and the patient is treated with these agents alone.
- Patients with NSAID-induced ulcers should be treated with **PPIs**, because these agents heal and prevent future ulcers more effectively than do H_2 receptor antagonists.
- PPIs are also used for **acute stress ulcers**.
- Acute stress ulceration often occurs in seriously ill patients who have an acute pathophysiological disturbance, such as hypotension, hypoxia, sepsis, uremia {high urea levels in the blood} or ischemia {restriction in blood supply to tissues}.

GASTROESOPHAGEAL REFLUX DISEASE – (GERD):

- H2 receptor antagonists are effective for the treatment of heartburn or GERD.
- H2 receptor antagonists act by decreasing acid secretion; therefore, they may not relieve symptoms of heartburn for up to 45 minutes.
- Antacids more quickly and efficiently neutralize stomach acid, but their action is short lived.
- For these reasons, **PPIs are now used preferentially in the treatment of GERD**, especially for patients with severe and frequent heartburn.

Pharmacokinetics:

- After oral administration, the H2 receptor antagonists are rapidly absorbed.
- They distribute widely throughout the body (including into breast milk and across the placenta).
- They are excreted mainly in the **urine**.
- Cimetidine, ranitidine, and famotidine are also available in intravenous formulations.
- The half-life of these agents may be increased in patients with renal dysfunction, and dosage adjustments are needed.
- Cimetidine, ranitidine, and famotidine undergo first-pass hepatic metabolism resulting in a bioavailability of approximately 50%.
- **Nizatidine** has little first-pass metabolism.

Gastrointestinal and Antiemetic Drugs

Drug	Relative Potency	Dose to Achieve > 50% Acid Inhibition for 10 Hours	Usual Dose for Acute Duodenal or Gastric Ulcer	Usual Dose for Gastroesophageal Reflux Disease	Usual Dose for Prevention of Stress-Related Bleeding
Cimetidine	1	400–800 mg	800 mg HS or 400 mg bid	800 mg bid	50 mg/h continuous infusion
Ranitidine	4–10	150 mg	300 mg HS or 150 mg bid	150 mg bid	6.25 mg/h continuous infusion or 50 mg IV every 6–8 h
Nizatidine	4–10	150 mg	300 mg HS or 150 mg bid	150 mg bid	Not available
Famotidine	20–50	20 mg	40 mg HS or 20 mg bid	20 mg bid	20 mg IV every 12 h

bid, twice daily; HS, bedtime.

- They are highly **selective** and do not affect H_1 or H_3 receptors (**cognition** disorders, modulate the release of other NT's in the brain; **histamine** release in the CNS triggers **excitatory** NT's release such as glutamate and acetylcholine by stimulation of H_1 receptors in the cortex).
- H2 antagonists reduce acid secretion stimulated by histamine as well as by gastrin and cholinomimetic (cholinergic) agents.

- H2 antagonists are especially effective at inhibiting **nocturnal** acid secretion (which depends largely on histamine).
- They have a modest impact on **meal-stimulated** acid secretion (which is stimulated by gastrin and acetylcholine as well as histamine).
- These drugs are commonly given twice daily.

CLINICAL USES:

1. Gastroesophageal reflux disease (GERD):

- Patients with **infrequent** heartburn or dyspepsia (fewer than three times per week) may take either antacids or intermittent H2 antagonists.
- H2 antagonists may be taken prophylactically before meals in an effort to reduce the likelihood of heartburn.

- **Frequent** heartburn is better treated with twice-daily **H2 antagonists** or **PPIs**.

2. Peptic ulcer disease:

- **PPIs have largely replaced H2 antagonists** in the treatment of acute peptic ulcer disease. Nevertheless, H2 antagonists are still sometimes used.
- **Nocturnal** acid suppression by H2 antagonists affords effective ulcer healing in most patients with uncomplicated gastric and duodenal ulcers (**Once daily at bed time**).
- For patients with ulcers caused by **aspirin** or other **NSAIDs**, the NSAID should be **discontinued**.
- If the NSAID must be continued for clinical reasons despite active ulceration, a **PPI** should be given instead of an H2 antagonist to more reliably promote ulcer healing.
- For patients with acute peptic ulcers caused by ***H pylori***, H2 antagonists **no longer** play a significant therapeutic role.

3. Dyspepsia:

- They are sometimes prescribed in dyspepsia (**indigestion;** discomfort, pain nausea and bloating), yet the results compared with placebo are not that convincing.

4. Prevention of bleeding from stress-related gastritis:

- The agents that increase intragastric pH (H2 antagonists or PPIs) reduce the incidence of clinically significant bleeding and should be administered to patients who are at high risk of gastrointestinal bleeding.
- For patients who are unable to receive enteral medications, either intravenous H2 antagonists or PPIs may be administered.
- **Continuous** infusion of H2 antagonists is preferred over **bolus** infusions.

Adverse effects:

In general, the H2 receptor antagonists are well tolerated (very safe).

- **Cimetidine** can have **endocrine** effects, such as gynecomastia and impotence in men, and galactorrhea (continuous release of milk) in women because it:
  - Inhibits binding of dihydrotestosterone to androgen receptors.
  - Inhibits metabolism of estradiol.
  - Increases serum prolactin levels.

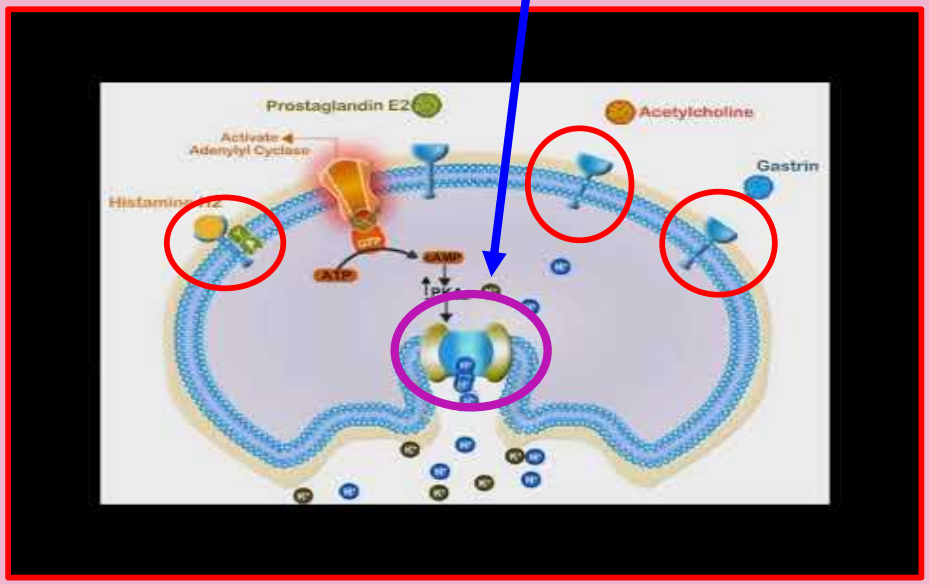
- **These effects are specific to cimetidine; don't occurs with other H2-antagonists.**

- **CNS-related:** such as confusion and altered mentation occur primarily in elderly patients and after intravenous administration.

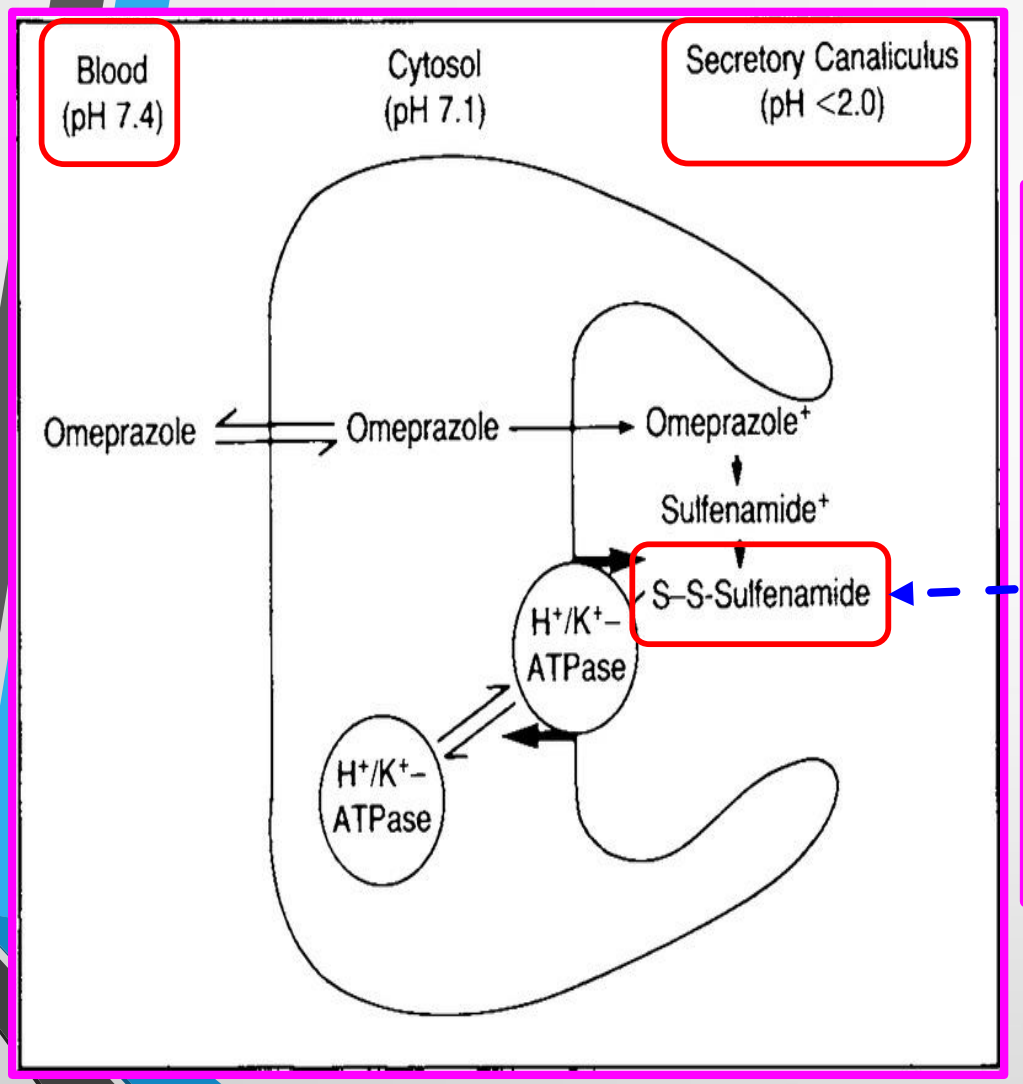
- H2 receptor antagonists may reduce the efficacy of drugs that require an acidic environment for absorption, such as ketoconazole {well dissoluted in acidic media as it is a weak base}.
- Cimetidine inhibits several cytochrome P450 isoenzymes and can interfere with the metabolism of many drugs, such as warfarin, phenytoin, and clopidogrel.
- H2 receptor blockers should not be administered to pregnant women unless necessary {don't have known harmful effects on the fetus}.
- Secreted into breast milk; can affect nursing infants.
- Rapid infusion can block cardiac H2 receptors; hypotension and bradycardia. Infuse over 30 minutes. (stimulation: increase in inotropic and chronotropic effects).

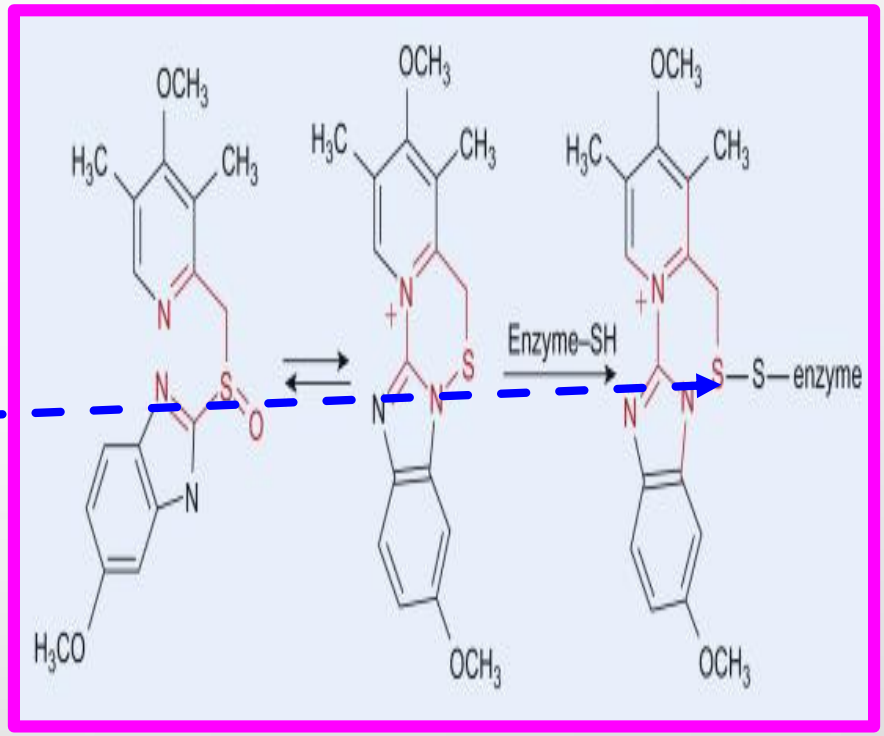
PROTON-PUMP INHIBITORS (PPIs):

- The PPIs bind to the **H+/K+-ATPase** enzyme system (proton pump) and suppress the secretion of hydrogen ions into the gastric lumen.
- The membrane-bound proton pump is **the final step** in the secretion of gastric acid; controls acid secretion apart from the source or the mechanism of the acid secretion.
- The available PPIs include:
  - Dexlansoprazole.
  - Esomeprazole.
  - Lansoprazole.
  - Omeprazole.
  - Pantoprazole.
  - Rabeprazole.



- These agents are prodrugs with an acid-resistant enteric coating to protect them from premature degradation by gastric acid.
- The coating is removed in the **alkaline duodenum**, and the prodrug, a **weak base**, is absorbed {unionized fraction} and transported to the parietal cell. There, it is converted to the active drug {sulfenamide; an isomer to omeprazole} and forms a stable covalent bond with the H+/K+-ATPase enzyme [see the figure, next slide].
- It takes about 18 hours for the enzyme to be resynthesized, and acid secretion is inhibited during this time.
- An oral product containing omeprazole combined with sodium bicarbonate for faster absorption [in the alkaline medium] and to protect the non-enteric coated drug from degradation in the acidic medium.


Blood
(pH 7.4)
Cytosol
(pH 7.1)
Secretory Canaliculus
(pH <2.0)
Omeprazole
Omeprazole
Omeprazole+
Sulfenamide+
S–S-Sulfenamide
H+/K+–
ATPase
H+/K+–
ATPase


OCH3
H3C
CH3
N
N
S
O
N
H3CO
OCH3
OCH3
H3C
CH3
N+
S
N
N
OCH3
OCH3
H3C
CH3
N+
S
N
N
Enzyme–SH
S—S—enzyme
OCH3

Therapeutic uses:

- The PPIs are superior to the H_2 antagonists in suppressing acid production and healing ulcers. Thus,

- They are the **preferred** drugs for the {1} treatment of GERD, {2} erosive esophagitis, {3} active duodenal ulcer, and pathologic hypersecretory conditions such as {4} Zollinger-Ellison syndrome [GASTRINOMA: tumor in the duodenum or pancreas; secretes large amounts of GASTRIN; hyperacidity].

- PPIs {5} reduce the risk of bleeding from ulcers caused by aspirin and other NSAIDs and may be used for {6} prevention or treatment of NSAID-induced ulcers.

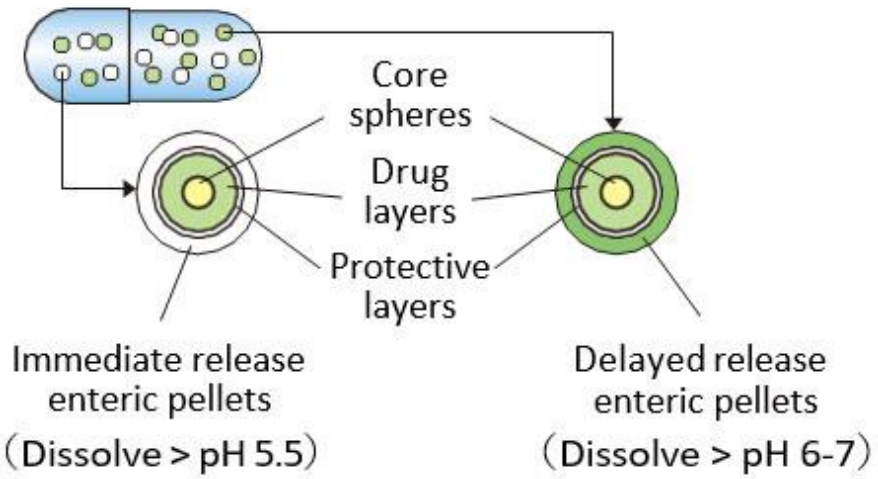
- PPIs are also used for {7} stress ulcer prophylaxis and management.

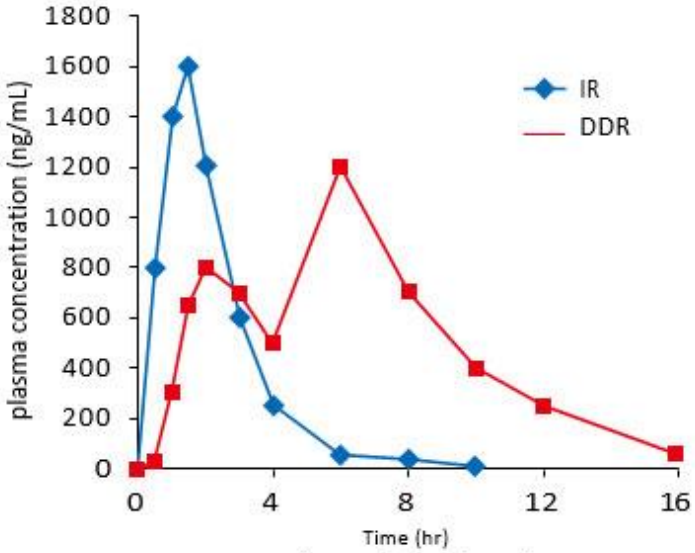
- PPIs are {8} combined with antimicrobial regimens used to eradicate *H. pylori*.

Pharmacokinetics:

- These agents are effective **orally**.
- For maximum effect, PPIs should be taken 30 to 60 minutes before breakfast or the largest meal of the day.
- Dexlansoprazole has a dual delayed-release formulation and can be taken without regard to food. {2 different sets of enteric-coated granules, see the figure on the next slide}.
- Esomeprazole, lansoprazole, and pantoprazole are available in intravenous formulations.
- Although the plasma half-life of these agents is only a few hours, they have a long duration of action due to covalent bonding with the H+/K+-ATPase enzyme.
- Metabolites of these agents are excreted in urine and feces.

Dual-delayed release of dexlanzoprazole





IR : Immediate release formulation
DDR : Dual delayed release formulation

ADVERSE EFFECTS:

- The PPIs are generally well tolerated.
- Omeprazole and esomeprazole may (1) decrease the effectiveness of clopidogrel [anti-platelet; it has to be activated] because they inhibit CYP2C19 and prevent the conversion of clopidogrel to its active metabolite.

✓ In general, concomitant use of these PPIs with clopidogrel is NOT recommended.

✓ However, if PPIs have to be prescribed to patients taking clopidogrel, agents with minimal CYP2C19 inhibition (pantoprazole or rabeprazole) may be preferred (3-study report).

- PPIs may increase the risk of (2) fractures, particularly if the duration of use is 1 year or greater.

- Prolonged acid suppression with PPIs (and H2 receptor antagonists) may result in **(3) low vitamin B12** because **acid** is required for its absorption in a complex with intrinsic factor [a glycoprotein produced by the parietal cells & is necessary for Vit B12 absorption].
- Elevated gastric pH may also **(4) impair the absorption of calcium carbonate.**

✓ **Calcium citrate** is an effective option for calcium supplementation in patients on acid suppressive therapy, since absorption of the citrate salt is not affected by gastric pH.

✓ **(5) Diarrhea** and **Clostridium difficile colitis** may occur in patients receiving PPIs. Patients must be counseled to **discontinue** PPI therapy if they have **diarrhea** for several days.

✓ **(6) Hypomagnesemia** {↓Mg}.

✓ **(7)** Increased incidence of **pneumonia**.

Prostaglandins:

- Their cytoprotective effects include:
  - Inhibition of acid secretion.
  - Stimulation of mucus and bicarbonate secretion.
- A deficiency of prostaglandins is thought to be involved in the pathogenesis of peptic ulcers. **Misoprostol**, an analog of prostaglandin E1, is approved for the prevention of **NSAID-induced gastric ulcers.**
- Prophylactic use of misoprostol should be considered in patients who take **NSAIDs** and are at moderate to high risk of NSAID-induced ulcers, such as elderly patients and those with previous ulcers.
- Misoprostol is contraindicated in pregnancy, since it can stimulate uterine contractions and cause miscarriage.

- Dose-related **diarrhea** is the most common adverse effect and limits the use of this agent.
- **Thus, PPIs are preferred agents for the prevention of NSAID-induced ulcers.**

Antacids:

- Antacids are (1) weak bases that react with gastric acid to form water and a salt to diminish gastric acidity.
- Because pepsin (a proteolytic enzyme; mucosal damage) is **inactive** at a pH greater than 4, (2) antacids also reduce pepsin activity.
- Antacid products vary widely in their chemical composition, acid-neutralizing capacity, sodium content, and palatability.

- Commonly used antacids are combinations of salts of **ALUMINUM AND MAGNESIUM**, such as aluminum hydroxide and magnesium hydroxide [$Mg(OH)_2$].
- **CALCIUM CARBONATE** [$CaCO_3$] reacts with HCl to form CO_2 and $CaCl_2$ and is also a commonly used preparation.
- Systemic absorption of **SODIUM BICARBONATE** can produce transient metabolic alkalosis and produce a significant sodium load. Therefore, this antacid is **not recommended**.

Therapeutic uses:

- Antacids are used for symptomatic relief of peptic ulcer disease, heartburn, and GERD.
- They should be administered after meals for maximum effectiveness.
- **Calcium carbonate** preparations are also used as **calcium supplements** for the prevention of osteoporosis.

Adverse effects:

- **Aluminum hydroxide** tends to cause constipation, whereas **magnesium hydroxide** tends to produce diarrhea, thus, preparations that combine these agents aid in normalizing bowel function.
- Accumulation and adverse effects may occur in patients with renal impairment.

MUCOSAL PROTECTIVE AGENTS:

- Also known as cytoprotective compounds.
- These agents have several actions that enhance mucosal protection mechanisms, thereby preventing mucosal injury, reducing inflammation, and healing existing ulcers.

1. Sucralfate:

- This complex of aluminum hydroxide and sulfated sucrose binds to positively charged groups in proteins of both normal and necrotic mucosa forming complex gels which act as a **physical barrier** that protects the ulcer from pepsin and acid, allowing the ulcer to heal.
- Although sucralfate is effective for the treatment of duodenal ulcers and prevention of stress ulcers, its use is limited due to:
  - The need for multiple daily dosing.
  - Drug–drug interactions.
  - The availability of more effective agents.
- Because it requires an acidic pH for activation, sucralfate should **not** be administered with PPIs, H_2 antagonists, or antacids.
- Sucralfate is well tolerated {constipation due to Al}.
- It can bind to other drugs and interfere with their absorption.

2. Bismuth subsalicylate:

- It is a component of **quadruple** therapy to heal *H. pylori*-related peptic ulcers.
- In addition to its {1} **antimicrobial** actions, {2} **it inhibits the activity of pepsin**, {3} **increases secretion of mucus**, {4} and **interacts with glycoproteins in necrotic mucosal tissue to coat and protect the ulcer.**

ADVERSE EFFECTS:

- All bismuth formulations have excellent safety profiles.
  - Bismuth causes **harmless blackening of the stool**, which may be confused with gastrointestinal bleeding.
  - **Harmless darkening of the tongue**.
  - Prolonged usage of some bismuth compounds may rarely lead to bismuth toxicity, resulting in **encephalopathy** (ataxia, headaches, confusion, seizures).

ANTIEMETIC AGENTS:

- Nausea and vomiting may be manifestations of a wide variety of conditions, including adverse effects from medications; systemic disorders or infections; pregnancy; vestibular dysfunction; central nervous system infection or increased pressure; peritonitis; hepatobiliary disorders; radiation or chemotherapy; and gastrointestinal obstruction, dysmotility {related to the muscles of the GIT}, or infections.
- Uncontrolled vomiting can produce dehydration, profound metabolic imbalances, and nutrient depletion.
- 10% to 40% of patients experience nausea and/or vomiting in anticipation of chemotherapy (anticipatory vomiting).
- Anticipatory vomiting: triggered by talking or thinking about the medication.

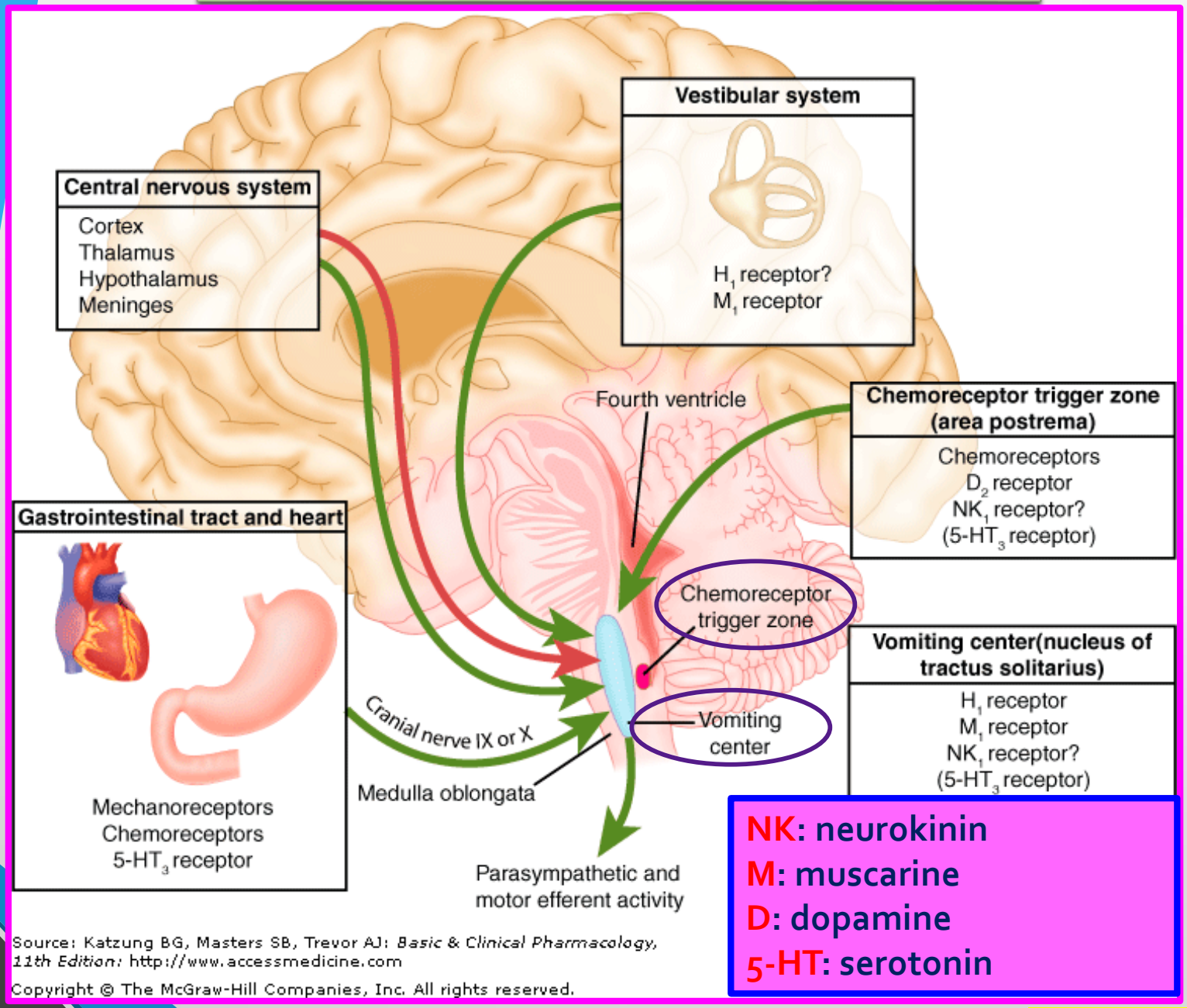
Pathophysiology:

- **Vomiting center**, brain stem neuronal region, coordinates the complex act of vomiting through interactions with cranial nerves VIII and X and neural networks in the nucleus tractus solitarius that control respiratory, salivatory, and vasomotor centers.
- High concentrations of muscarinic M1, histamine H1, neurokinin 1 (NK1), and serotonin 5-HT3 receptors have been identified in the **vomiting center**.
- There are four important sources of **afferent** input to the vomiting center:

1. The "chemoreceptor trigger zone":

- Outside the BBB.
- D_2 receptors, opioid receptors, 5-HT_3 and NK_1 receptors.

Gastrointestinal and Antiemetic Drugs



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

NK: neurokinin
M: muscarine
D: dopamine
5-HT: serotonin

2. The vestibular system {of the inner ear}:

- A sensory system that is responsible for providing the brain with information about **motion**, **head position**, and **spatial orientation.**
- Important in **motion sickness** via cranial nerve VIII.
- It is rich in muscarinic M1 and histamine H1 receptors.

3. Vagal and spinal afferent nerves:

- From the gastrointestinal tract.
- Rich in 5-HT3 receptors.
- Irritation of the gastrointestinal mucosa by chemotherapy, radiation therapy, distention, or acute infectious gastroenteritis leads to release of mucosal **serotonin** and activation of these receptors.

4. The central nervous system:

- Vomiting due to psychiatric disorders, stress, and anticipatory vomiting prior to cancer chemotherapy.

❖ Due to the complexity of the mechanisms involved in emesis, the antiemetics represent a variety of classes.

CLASSES OF THE ANTIEMETIC AGENTS:

1. Phenothiazines:

- Such as prochlorperazine.
- Act by blocking dopamine receptors in the CTZ.
- Prochlorperazine is effective against low or moderately emetogenic chemotherapeutic agents (e.g. fluorouracil and doxorubicin).

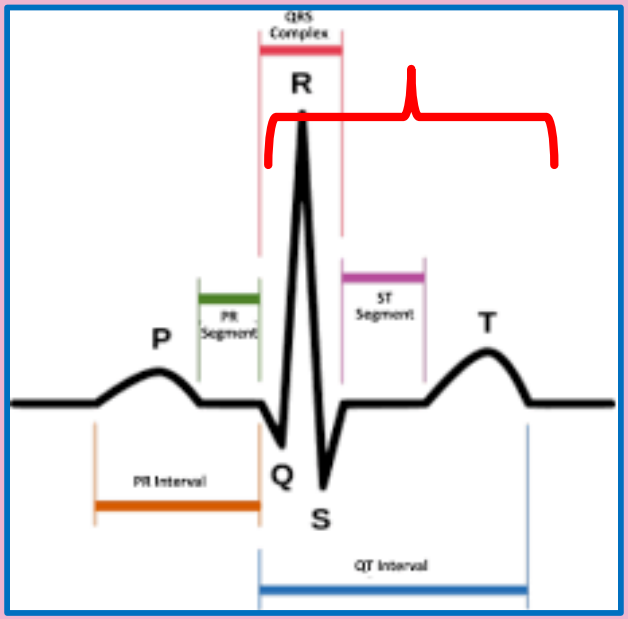
2. 5-HT3 receptor blockers:

- The 5-HT3 receptor antagonists include dolasetron, granisetron, ondansetron, and palonosetron.
- They are important in treating chemotherapy-induced nausea and vomiting (CINV), because of their superior **EFFICACY** and **LONGER DURATION OF ACTION**.
- These drugs can be administered as a single dose prior to chemotherapy (i.v. or orally).

PHENOTHIAZINES
Prochlorperazine GENERIC ONLY
5-HT$_3$ SEROTONIN RECEPTOR ANTAGONISTS
Dolasetron ANZEMET
Granisetron SANCUSO, SUSTOL
Ondansetron ZOFRAN
Palonosetron ALOXI
SUBSTITUTED BENZAMIDES
Metoclopramide REGLAN
BUTYROPHENONES
Droperidol GENERIC ONLY
Haloperidol HALDOL
BENZODIAZEPINES
Alprazolam XANAX
Lorazepam ATIVAN
CORTICOSTEROIDS
Dexamethasone DECADRON
Methylprednisolone MEDROL
SUBSTANCE P/NEUROKININ-1 RECEPTOR ANTAGONIST
Aprepitant, Fosaprepitant EMEND
*Netupitant** AKYNZEO
Rolapitant VARUBI

- They are efficacious against all grades of emetogenic therapy.
- **Ondansetron** and **granisetron** prevent emesis in 50% to 60% of **cisplatin**-treated patients.
- Extensively metabolized by the liver, excreted in the urine.
- **QT prolongation** can occur with high doses of ondansetron and dolasetron.

QT prolongation: is a measure of delayed ventricular repolarisation, which means the heart muscle takes longer than normal to recharge between beats.
Excessive QT prolongation can trigger tachycardias such as Torsades de Pointes (TdP) {ventricular tachycardia}.



3. Substituted benzamides:

- Metoclopramide, is effective at high doses against the emetogenic **cisplatin**.
- Metoclopramide accomplishes this through inhibition of dopamine in the CTZ {blocking D2 recptors}.
- **Antidopaminergic adverse effects**, including **extrapyramidal** symptoms [Spasm of tongue, neck, face and back / tremors, heavy gait / repetitive motion and agitation] limit long-term and high-dose use.
- Metoclopramide enhances gastric motility and is useful for patients with gastroparesis [motility is slowed down or doesn't work at all, preventing the stomach from emptying properly].

4. Butyrophenones:

- **Droperidol** and **haloperidol** act by blocking dopamine receptors.
- The butyrophenones are moderately effective antiemetics.
- Droperidol had been used most often for sedation in endoscopy and surgery, usually in combination with opioids or benzodiazepines.
- However, it may **prolong the QT-interval** and should be reserved for patients with inadequate response to other agents.

5. Benzodiazepines:

- The antiemetic potency of lorazepam and alprazolam is **LOW**.
- Their beneficial effects may be due to their **SEDATIVE**, **ANXIOLYTIC**, and **AMNESTIC** properties

6. Corticosteroids:

- **DEXAMETHASONE** and **METHYLPREDNISOLONE**, used alone, are effective against mildly to moderately emetogenic chemotherapy.
- Most frequently, they are used in combination with other agents.
- Their antiemetic mechanism is not known, but it may involve blockade of prostaglandins.

7. Substance P/neurokinin-1 receptor antagonists:

- It is a neuropeptide (11 amino acids), acting as a NT and as a neuromodulator.
- **APREPITANT**, **NETUPITANT** and **ROLAPITANT** target the **neurokinin receptor** in the vomiting center and block the actions of **substance P**, {that is related to neurokinin A =**substance K**)}.

- **Fosaprepitant** is a prodrug of **aprepitant** that is administered intravenously.
- These oral agents are indicated for highly or moderately emetogenic chemotherapy regimens.
- They are usually administered with dexamethasone and a 5-HT3 antagonist.
- Unlike most 5-HT3 antagonists, these agents are effective for the **delayed** phase of CINV, which occurs 24 hours or more after chemotherapy. {**CINV:** chemotherapy-induced nausea and vomiting}
- Aprepitant and rolapitant undergo hepatic metabolism, primarily by CYP3A4.
- Coadministration with strong **inhibitors** or **inducers** of CYP3A4 (for example, **clarithromycin** or **St. John's wort**, respectively) should be avoided.

- **Aprepitant** is an inducer of CYP3A4 and CYP2C9, and it also exhibits dose-dependent inhibition of CYP3A4.
- **Rolapitant** is a moderate inhibitor of CYP2D6.

ADVERSE EFFECTS:

- Fatigue, diarrhea, abdominal pain, and hiccups [an involuntary spasm of the diaphragm and respiratory organs, with a sudden closure of the glottis and a characteristic sound like that of a cough].

COMBINATIONS OF ANTIEMETIC AGENTS AIM TO:

1. Increase efficacy.
2. Decrease toxicity and side effects.

THE END

REFERENCES:

- Basic and clinical pharmacology textbook 14th edition, 2018. Katzung.
- Lippincott's Illustrated Reviews, Pharmacology textbooks 5th, 6th and 7th editions, R. Harvey.
- Medscape - (https://www.medscape.com/).
- DrugBank - (https://www.drugbank.ca/).
- WebMD - (https://www.webmd.com/).
- Drugs.com - (https://www.drugs.com/).
- Healthline - (https://www.healthline.com/).
- RxList - (https://www.rxlist.com/script/main/hp.asp).
- NHS - (https://www.nhs.uk/).