GIS 2

PHARMACOLOGY

Done by: Lana Mango

Scientific Correction: حافظ حمام

Gramatical Correction: Lana Mango

Doctor: Hamzeh Elayan

This sheet isn't as long as it looks. There's a couple of summaries and notes.
Any additional info that I added for further clarification will be written as a "Side Note" or a quick reminder.
The professor mentioned EVERYTHING written in the slides.

Neutralization of Acids Using Antacids

- What are **Antacids**?

Antacids are non-prescription remedies that are used to treat:

1. **Heartburn**
2. **Dyspepsia**

> **Side note:**
> Dyspepsia: Indigestion

- Taken ***1 hour after*** a meal
- **Effect:** Neutralizes gastric acidity for up to ***2 hours***

Types of antacids:

1. Aluminum Antacids

- Cause:

a) Constipation
b) Interference with drug absorption

- **$AL(OH)3 + HCl \rightarrow ALCl3 + H2O$**

> **Al(OH)3 "aluminum hydroxide"** Does not produce CO2 → DOES NOT CAUSE DISTENTION OR BLOATING (Advantage)

2. Magnesium Antacids

Cause:

a) Diarrhea (because they have laxative action)
b) **Ionic Magnesium** stimulates Gastric release (Acid rebound)

> **Side Note: Acid rebound** is a condition in which the stomach produces even more acid after the consumption of foods and drinks.

- **$2HCl + Mg(OH)2 \rightarrow MgCl2 + 2H2O$**

> **Mg(OH)2 "magnesium hydroxide"** Does not produce CO2 → DOES NOT CAUSE DISTENTION OR BLOATING (Advantage)

- **Magnesium Trisilicate: Slow-acting Antacid** (Effect lasts for a longer period of time)

(To prevent the occurrence of Diarrhea or Constipation by Aluminum antacids): most commonly we have a combination of Aluminum and Magnesium Antacids

3. Calcium Carbonate "mineral source of chalks":

- **Should be avoided. Why?**
  a) Calcium can cause acid rebound **(Quick reminder: Ionic magnesium antacids cause acid rebound too)**
  b) Excessive chronic use → Milk-alkali syndrome
  With elevation of: SERUM CALCIUM, PHOSPHATE, UREA, NITROGEN, CREATININ & BICARBONATE levels.

- **$2HCl + CaCO_3 \rightarrow CaCl_2 + CO_2 + H_2O$**

Produces CO_2 → Causes bloating and distention **(unlike Al and Mg antacids)**

4. Sodium Bicarbonate

- Quick acting (Short duration of action) **- unlike Magnesium Trisilicate, which is slow-acting –**
- Followed by acid rebound
- **Should be avoided. Why?**
  a) Aggravates **CHF (chronic heart failure)**
  b) Counteracts diuretic therapy of hypertension **(Since it contains Na+)**
- Produces CO_2 → Causes **distention and belching**
- Highly absorbed → Causes **metabolic alkalosis**

- **$NaHCO_3 + HCl \rightarrow NaCl + H_2O + CO_2$**

Produces CO_2 → Causes bloating and distention **(unlike Al and Mg antacids)**

H2-Receptor Antagonists

Discovered in the 70's and revolutionized the treatment of Peptic Ulcers. (First drug ever used to treat peptic ulcers)

- Rapidly absorbed by the intestine.

1. **Cimetidine**
2. **Ranitidine**
3. **Famotidine**
4. **Nizatidine**

Cimetidine, Ranitidine and Famotidine:
Have low bioavailability (50%) due to first pass effect.

Nizatidine:
Has little first-pass effect

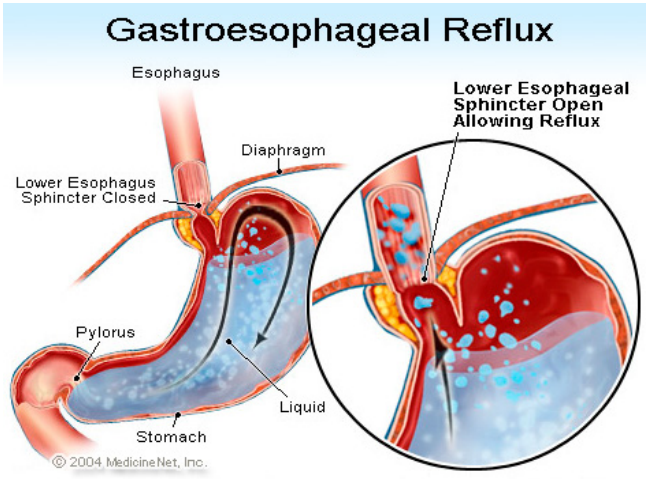
Duration of action:

- 6-10 hours
- **Taken twice/day**

Effect: (on nocturnal acid, daytime and meal stimulated acid secretions)

1. Inhibits **90% of nocturnal acid**
   NOTE: **Nocturnal acid** depends on histamine
2. Has modest impact on **meal-stimulated acid secretion**
   NOTE: Meal stimulated acid secretion is stimulated by gastrin, Ach and Histamine
3. Inhibits **60% of day-time meal stimulated acid**
4. OVERALL inhibition of **24-hr acid secretion** by **60-70%**

Uses:



1. GERD

- Taken prophylactically before meals

- **For EROSIVE ESOPHAGITIS:**

➢ Antagonist healing is <50%
➢ PPI are preferred

2. Non-Ulcer Dyspepsia (indigestion)

- Taken over the counter
- Treats intermittent dyspepsia that is not caused by Peptic Ulcer

3. Prevention of bleeding from stress-related Gastritis

- IV H2 antagonists
- **IV H2 antagonists are preferred over VI PPI**'s, due to their:
  - proven efficacy
  - Lower cost

4. Peptic Ulcer Disease

- H2 receptor antagonists have been **replaced by PPI** for PUD treatment
- Healing rate is >80-90% after 6-8 weeks
- Are not effective against PUD, in two cases:
  1. IF H Pylori is involved
  2. If NSAID's aren't stopped, and are continued to be taken

Adverse Effects of H2 antagonists

- Extremely Safe
- In 3% of cases/patients: Diarrhea, fatigue, myalgia, constipation

- **Cimetidine** is the only one that causes:
  - **In men:** Gynecomastia and impotence (due to its androgenic effect)
  - **In women:** Galactorrhea and sometimes menstrual disturbances

Drug Interactions:

1. **Cimetidine:**
- Inhibits cytochrome P450 enzyme → Increases t1/2 of many drugs
2. **Ranitidine:**
- Binds 4-10 times less than cimetidine. So, it is less likely to produce/have such interactions.
3. **Nizatidine and Famotidine:**
- Binding is negligible → **NO EFFECT ON CYT P450**

PPI (Proton Pump Inhibitors)

Among the most widely prescribed drugs worldwide due to their outstanding efficacy and safety.

- **All of the PPI's are Prodrugs,** released in the intestine (Destroyed by stomach acid).
- **PPI's and their route of administration:**

Omeprazole	Oral
Rabeprazole	Oral
Esomeprazole (Nexium)	Oral AND IV
Lansoprazole	Oral AND IV
Pantoprazole	Oral AND IV

Side note: **ORal only: Omeprazole, Rabeprazole**

- **Pantoprazole (oral and IV).**
  are tablets with a pH-sensitive coating.

pH sensitive coating: Dissolves only in alkaline medium in the intestine.

The capsule does not dissolve in the acidic environment of the stomach, and so the drug isn't released in the stomach.

- **Esomeprazole** (**Nexium**) **(oral and IV).**
  available as capsules of **enteric-coated granules.**

All PPIs are destroyed by the acidity of the stomach. So, the drug must bypass the stomach in any way possible. So, the ***capsule of enteric-coated granules*** allows the drug to be released in the intestine so that their absorption takes more time, and to protect it from the acidity of the stomach

- **Immediate-Release Omeprazole** contains ***sodium bicarbonate*** to protect the drug from acid **degradation**, which results in rapid response.

Immediate release omeprazole: It usually takes these drugs a longer time to get to intestine, and so they don't have a rapid response. ***As for immediate release omeprazole***, it has a capsule that contains sodium carbonate. This helps:
- **protect the drug from acid degradation**
-This means that it takes **less time for the drug to be absorbed →producing a more rapid response.**

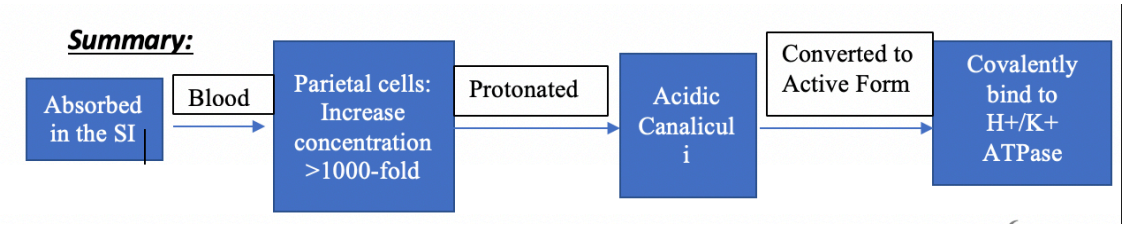
- All PPI's are weak lipophilic bases

Mechanism of action:

1. All PPI's are absorbed in the small intestine
2. They are then delivered to parietal cells through the blood.
3. This is where they are protonated and trapped in acidic canaliculi
4. Their concentration increases >1000-fold in the parietal cells
5. The drug is then converted to its Active Form
   (Quick reminder: PPI's are prodrugs that are later converted to their active forms)
6. This active form binds to the H+/K+ ATPase (Proton Pump) enzyme covalently, and inactivates it

- They have short half-lives, but their effect lasts for **24 hours**

How come? Once the enzyme is inactivated, the body must produce new enzymes. This requires **at least 18 hours** to synthesize new proton pump molecules.



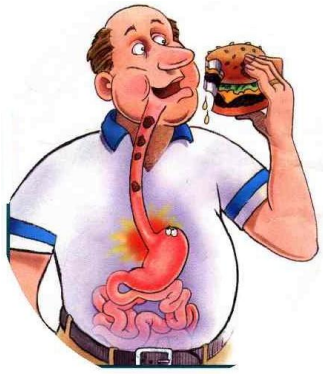
PPI Acid Inhibition:

- PPIs inhibit both **fasting** and **meal-stimulated** secretions
- Inhibits **(90-98%) of 24-hour secretion**
- The full acid-inhibiting potential is reached in **3-4 days**
- Usually are taken once daily about **30 min -1**h before meal

Clinical Uses of PPIs

1. **Gastroesophageal Reflux (GERD)**:

- They are the most effective agents used to treat all forms of GERD

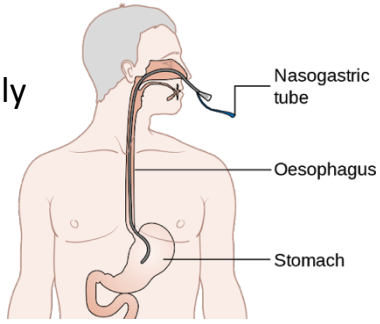


2. **Non-ulcer Dyspepsia:**

- Modest activity.
- 10 - 20% more beneficial than a placebo (Not that effective)
- Not worth the price
- Cheaper alternative: **Antacids**

3. **Stress- Related Gastritis:**

- **Immediate- release omeprazole** is administered orally by a **nasogastric tube. (image on the right for clarification)**
- For patients without a nasoenteric tube, IV H2-blockers are preferred because of their proven efficacy.



With Nasogastric tube → **Immediate release Omeprazole**
Without Nasogastric Tube → **IV H2 blockers**

4. **Gastric acid hypersecretory states, including Zollinger -Ellison syndrome**

- Usually **high doses of omeprazole** (oral) are used.

5. **Peptic Ulcer Disease:**

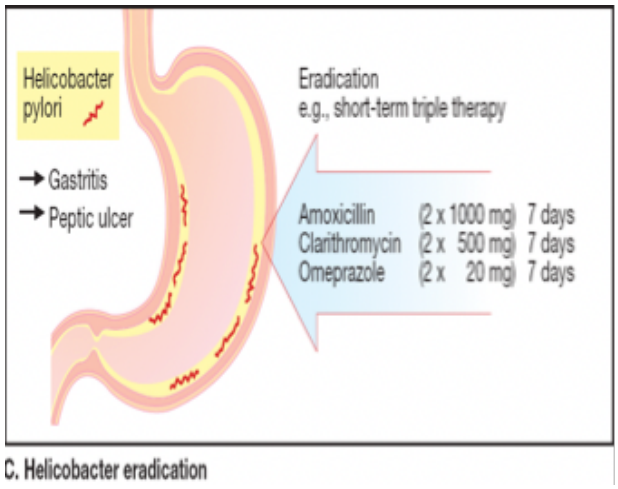
- PPI's heal >90% of cases within 4-6 weeks

1) H. Pylori - associated ulcers:

- PPIs eradicate **H. pylori** by:
  - **Direct antimicrobial activity**
  - By **lowering MIC** -*Minimum Inhibitory Concentration*- of the antibiotics.

- Triple Therapy: 3 drugs are used simultaneously: -
  1. **PPI** twice daily (omeprazole)
  2. **Clarithromycin** 500 mg twice daily
  3. **Amoxicillin** 1g twice/day **OR** **Metronidazole** 500mg twice/day

Within 1-2 weeks → Ulcer heals, and microbe is killed



C. Helicobacter eradication

Side Note/Reminder:

Difference between H2 blockers and PPIs:

- **H2 blockers** → **INEFFECTIVE** against H Pylori Associated PUD
- **PPIs** → **EFFECTIVE** against H Pylori Associated PUD

2) NSAID-associated ulcers:

- Healing despite continued NSAID use

Unlike H2 receptor antagonists, which aren't effective against PUD if continued use of NSAID's isn't stopped

- Also used to prevent ulcer of NSAIDs
- If a patient is suffering from Arthritis and needs to take NSAIDs, PPI's are prescribed along with the NSAID's to prevent NSAID-associated ulcers from developing.

3) Rebleeding peptic ulcer:

a. **Oral or IV.** PPI's:
   - Provide High pH
   - This enhances coagulation and platelet aggregation

Adverse Effects of PPIs:

- **Well tolerated.**
- **Cause**:
  1. Headache
  2. Diarrhea
  3. Abdominal pain
  4. Nausea
  5. Dizziness
  6. Reduction of **cyanocobalamin (vitamin B12)** absorption:
     Acid is needed for vitamin B12 to be freed from the protein it's attached to. If PPIs are used → Low acid secretion → The vitamin does not detach from the protein → It is not absorbed

To clarify (side note):
First, hydrochloric **acid** in the stomach separates **vitamin B12** from the **protein** to which **vitamin B12** is attached in food.
After this, **vitamin B12** combines with a **protein** made by the stomach called **intrinsic factor** and is absorbed by the body.

  7. Increased risk of **GI and pulmonary infection:**
     Hydrochloric acid is the first line of defense against bacteria. Without it → More prone to get infected
  8. Increased **serum gastrin levels** cause:
- **Chronic inflammation in gastric body.**
- **Atrophic gastritis and intestinal metaplasia**.

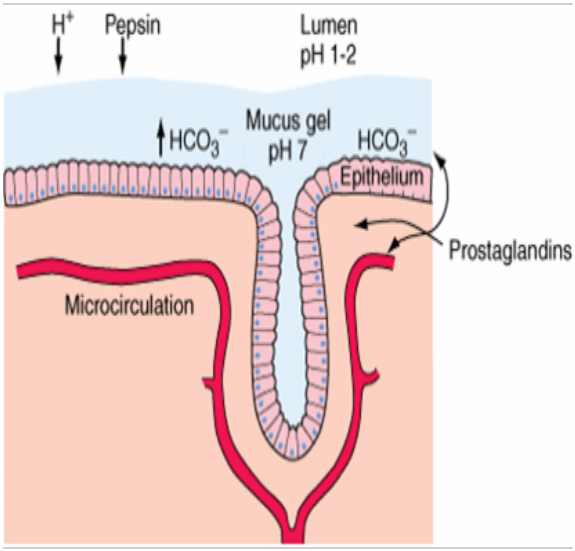
➢ There is no evidence to prove that PPI's are associated to cancer.

Drug Interactions:

Decreased gastric acidity may affect absorption of drugs that depend on the acidity of the stomach, such as:

1. Digoxin
2. Ketoconazole

Mucosal Protective Agents



1. *Both **mucus and epithelial cell-cell tight junctions** restrict back diffusion of acid and pepsin.*
2. *Epithelial **bicarbonate** secretion.*
3. ***Blood flow** carries bicarbonate.*
4. *Injured epithelium is repaired by **restitution** (restoration)*
5. *Mucosal **prostaglandins** stimulate:*
   >**Mucus and bicarbonate secretion**
   >**Mucosal blood flow.**

Sucralfate

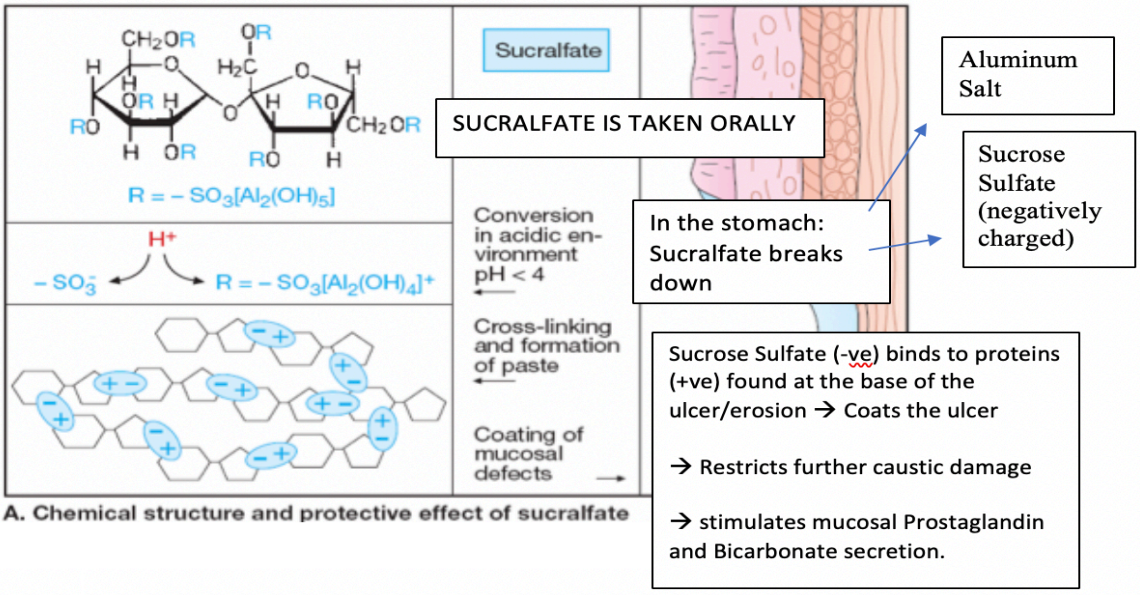
Complex of **Sucrose Salt** and **Sulfated Aluminum hydroxide**

- Taken orally → Breaks down in the stomach into → **sucrose sulfate** (which has a strong negative charge) and an **aluminum salt.**

In the stomach: Sucralfate –Broken down→ Aluminum Salt + **Sucrose Sulfate**

- Sucrose Sulfate (negatively charged) binds to proteins (positively charged) found at the base of the ulcer/erosion → Coats the ulcer, forming a protective physical layer → Restricts further caustic damage → stimulates mucosal Prostaglandin and Bicarbonate secretion.

<u>Again</u>:



A. Chemical structure and protective effect of sucralfate

- Duration of action → 6 Hours
- Less than 3% of intact drug and aluminum is absorbed.

Clinical Uses

1 g taken 4 times/day on an **empty stomach** (through a nasogastric tube)

1. **Reduces the incidence of upper GI bleeding** in **critically ill patients hospitalized in the intensive care unit.**
2. **Prevention of stress-related bleeding** because acid inhibitory therapies (including PPIs) **may increase the risk of nosocomial pneumonia** (an infection of the lungs that occurs during a **hospital** stay).

Remember, since stomach acidity decreases → microorganisms aren't killed → Increase risk of infection

Adverse Effects

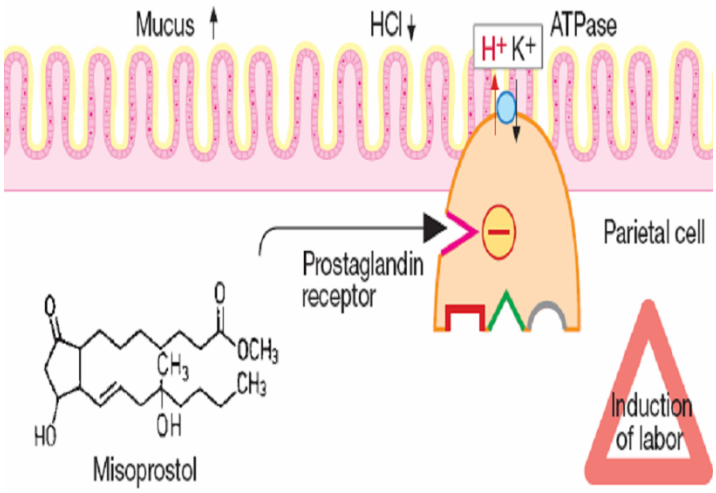
- Not absorbed, so no systemic adverse effects.
- Constipation (2% of patients) due to the aluminum salt.
- Caution in renal insufficiency. (Aluminum absorbed → Renal insufficiency)

Drug Interactions

Sucralfate may bind to other medications, impairing their absorption.

Prostaglandin Analogs

Misoprostol



- A methyl analog of **PGE1.**
- **Half-life**: less than **30 min**
- **Administered: 3-4 times daily**.

Actions:

1. Stimulates **mucus** and **bicarbonate** secretion.
2. Enhances **mucosal blood flow.**

3. Acts **on parietal cells**, reducing histamine-stimulated cAMP production → causing **modest acid inhibition**.
4. Stimulates **intestinal** electrolyte & fluid secretion,
5. Increase intestinal motility
6. **Uterine contractions**.

Clinical Uses of Prostaglandin Analogs:

1. **Prevention of NSAID-induced ulcers** in high-risk patients.

   NOTE: Not widely used for this purpose for many reasons:

   1. Side effects
   2. Need for multiple daily dosing.
   3. **PPI** may be as effective and better tolerated (fewer side effects)
   4. **Cyclooxygenase2-selective NSAIDs** are an option for such patients**. (they don't interfere with Prostaglandin synthesis in the stomach)**

Adverse Effects & Drug Interactions

1. Diarrhea and cramping abdominal pain (10–20% of patients)
2. It should not be used during pregnancy (Could lead to miscarriage)

-No significant drug interactions.

Colloidal Bismuth Compounds: A mucosal protective agent, provides coat on the ulcer.

1. **Bismuth subsalicylate**
2. **Bismuth subcitrate.**

- Bismuth is minimally absorbed from GIT (< 1%).
- **Effect**:

  1. Reduce the gastric HCL secretion
  2. Help in eradication of H. pylori
  3. Stimulates the PGE secretion
  4. Reduce pepsin secretion
  5. Decrease H+ ion back diffusion.

- **Bismuth subsalicylate** reduces stool frequency and liquidity in acute infectious diarrhea, due to salicylate inhibition of intestinal prostaglandin and chloride secretion.

    6. Has direct antimicrobial effects & binds enterotoxins, so useful in preventing & treating **traveler's diarrhea** (commonly occurs in people who travel long distances after ingestion or intake of contaminated food -E. coli-)
    7. Widely used for the nonspecific treatment of **dyspepsia** and **acute diarrhea**.
    8. Has direct antimicrobial activity against *H pylori and* used as second-line therapy for the eradication of *H pylori* infection

        - **If the first treatment or therapy fails: take PPI with bismuth subsalicylate, tetracycline and metronidazole for 10–14 days).**

Adverse Effects

1. Bismuth blackens the stool and the tongue.
2. Prolonged usage may rarely lead to bismuth toxicity → Leads to **encephalopathy**.