بسم الله الرحمن الرحيم

PHARMACOLOGY

FINAL | Lecture #2

PPIs & Laxatives (Pt. 1)

Written by: Sara Qudaisat
Sara Masadeh

Reviewed by: Sara Masadeh
Sara Qudaisat

﴿ وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم ﴾

اللهم استعملنا ولا تستبدلنا

Quiz on the previous lecture

https://docs.google.com/forms/d/e/1FAIpQLSeSS9Yuk6Jdl5Ab05E5zL7rp2O01qP49M4Cnl55Ecy32i83FA/viewform

Proton Pump Inhibitors

Proton Pump Inhibitor Drugs

Proton pump inhibitor drugs have many different trade names and are manufactured by different pharmaceutical companies in the market

Proton Pump Inhibitors, PPI(1990s)

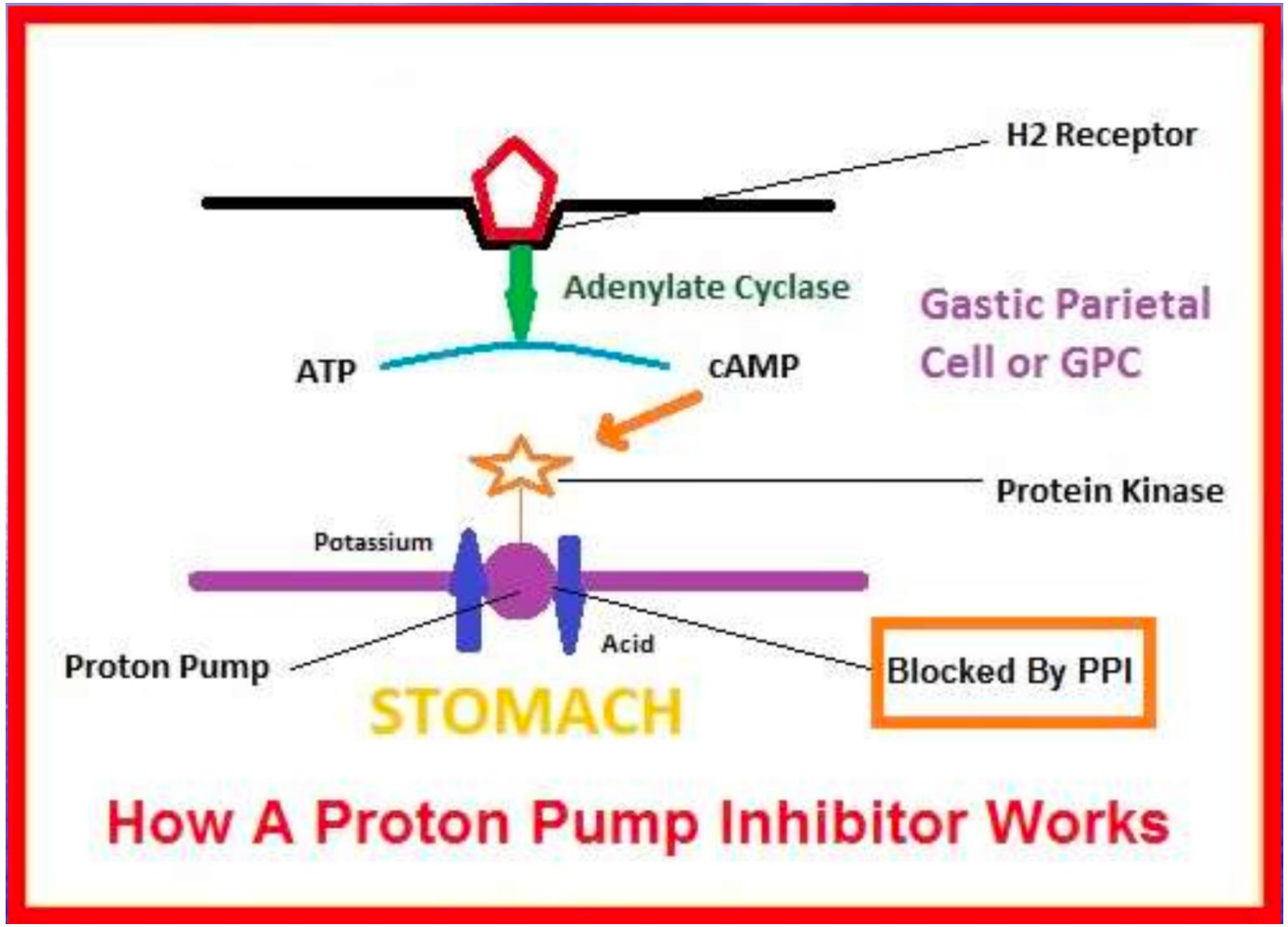
- Very efficacious and safe drugs.

They present in different classes:

- Omeprazole (oral).
- Rabeprazole (oral).
- Lanzoprazole (oral and IV).
- Pantoprazole (oral and IV).
- Esmoprazole (oral and IV).
- Formulated mainly as a prodrug which is released in the intestine.
- Some formulas of PPI drugs are in the form of Immediate-Release Suspension which results in rapid response (rapid onset of action). However, they are considered less common in comparison with the prodrug formula.

PPIs VS H2 Receptor Antagonist

H2 receptor antagonist blocks the receptor which blocks the downstream pathway (recall from physiology that when histamine binds to H2 receptors present at the parietal cells this will elevate cAMP levels in the cell enhancing the production of HCL and inducing peptic ulcers)



Proton pump inhibitors bind to the H+/K+- ATPase enzyme system (proton pump) of the parietal cell and suppress the secretion of hydrogen ions into the gastric lumen, thereby reducing the acidity of the stomach

Pharmacokinetics

- They are lipophilic weak bases (pKa 4-5).
- After intestinal absorption, they diffuse across lipid membranes into acidified compartments such as the parietal cell canaliculus.
- After their absorption, the prodrug becomes protonated and concentrated more than 1000-fold within the parietal cells.
- There, it undergoes a molecular conversion to the active form -which is responsible of the drug's effect on the proton pumps-which covalently binds the H+/K+ ATPase enzyme and inactivates it, thereby preventing pumping protons and increasing the acidity.

Pharmacokinetics

- Rabeprazole has immediate release, while omeprazole have faster onsets of action.
- These drugs should be given one hour before meal.
- Have short half lives but effect lasts for 24 hours (given once daily)due to irreversible inhibition.

Pharmacodynamics

- Inhibit both fasting and meal-stimulated secretion because they block the final common pathway of acid secretion (90-98% of 24-hour secretion).

This dual inhibition guarantees more efficient effect of PPIs

Clinical Uses

- Gastroesophageal Reflux (GERD):
  - They are the most effective agents in all forms of GERD and complications.
- Nonulcer Dyspepsia:
  - Modest activity.
  - 10-20% more beneficial than a placebo.

Clinical Uses

- Stress-Related Gastritis:
  - Oral immediate- release omeprazole administered by nasogastric tube.
  - For patients without a nasoenteric tube, IV H2-antagonists are preferred because of their proven efficacy.
  - In all cases of stress-related ulcers the PPIs are considered an effective treatment
- Gastrinoma and other Hypersecretory Conditions:
  - Usually **high doses** of omeprazole are used.

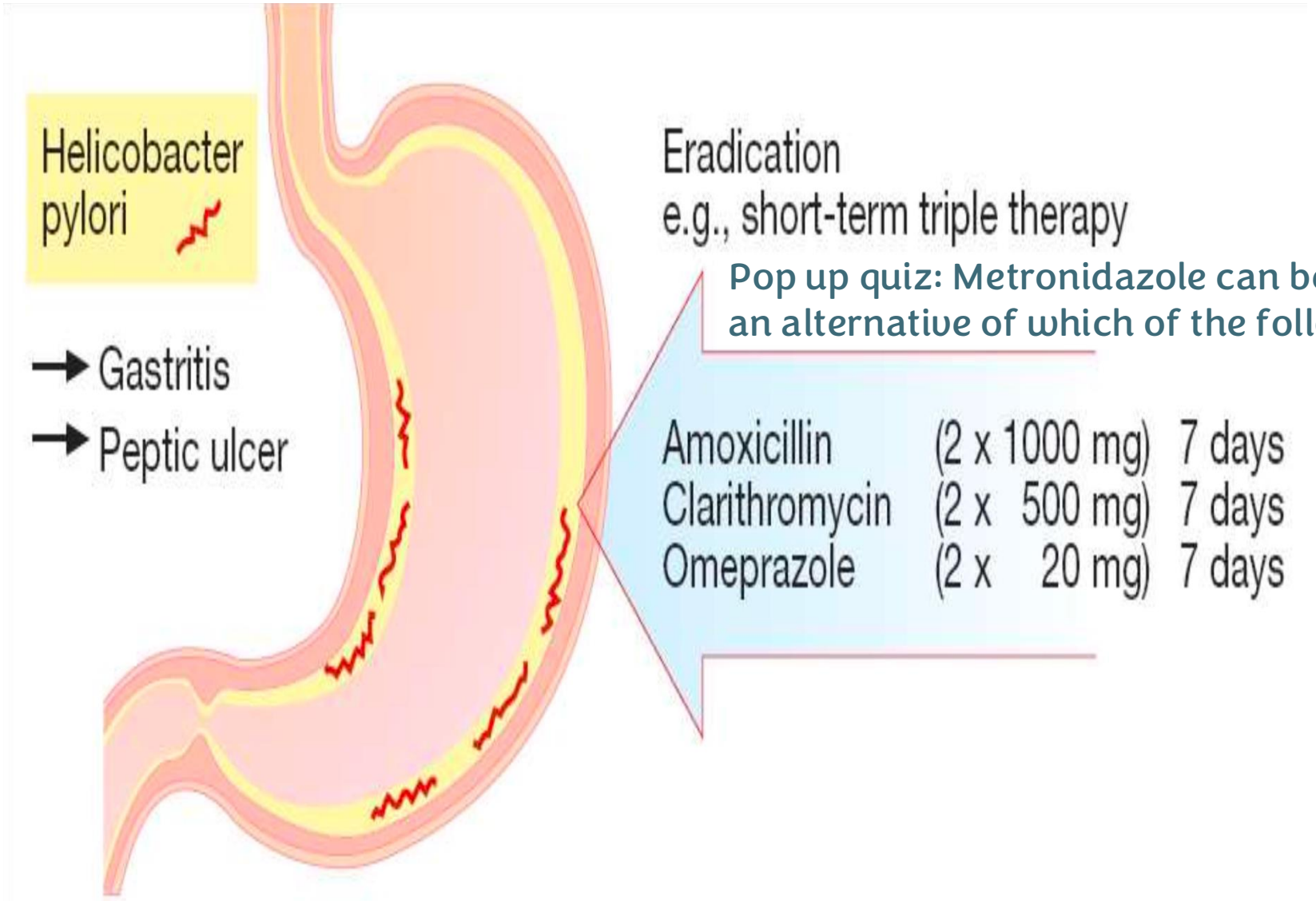
Clinical Uses

- Peptic Ulcer Disease:
  - They heal more than 90% of cases within 4-6 weeks.
  - *H.pylori* - associated ulcers:
    - Besides the role of (1)PPIs in reducing acidity, they (2)eradicate *H. pylori* by direct antimicrobial activity and by lowering MIC of the antibiotics.
    - Triple Therapy:
      - PPI twice daily.
      - Clarithromycin 500mg twice daily.
      - Amoxicillin 1gm twice daily ,OR, Metronidazole 500mg twice daily.

Note that 1 and 2 are the mechanisms by which the PPIs treat the peptic ulcers

MIC:Minimum Inhibitory Concentration

H. Pylori Eradication Therapy



Pop up quiz: Metronidazole can be used as an alternative of which of the following?

Check the previous slide of the right answer

Clinical Uses

- Peptic Ulcer Disease:
  - NSAID-associated ulcers:
    - PPIs promote ulcer healing despite continued NSAID use.
    - Also used to prevent ulcer complications of NSAIDs.
  - Rebleeding peptic ulcer:
    - Oral or IV.
    - High pH caused by peptic ulcers may enhance coagulation and platelet aggregation therefore stopping the bleeding process.

Adverse Effects

General:

- Diarrhea, headache (normal adverse effects associated with PPI use), abdominal pain, not teratogenic in animals, but not used in pregnancy.
- Reduction of cyanocobalamine (vitamin B12) absorption. This results in an increased risk of GI and pulmonary infection as vitamin B12 can help balance immune responses to better fight viral and bacterial infections. The solution is to take vitamin B12 supplements from time to time while using PPIs.

Adverse Effects

Increased serum gastrin levels can lead to cancer-inducing conditions such as:

- Hyperplasia of ECL cells.
- Carcinoid tumors in rats, but no such findings were recorded in humans.
- Increase proliferative rate of colonic mucosa.
- Chronic inflammation in gastric body.
- Atrophic gastritis and intestinal metaplasia.

Gastritis is a general term for a group of conditions with one thing in common:

Inflammation of the lining of the stomach.

A change of cells to a form that does not normally occur in the tissue in which it is found

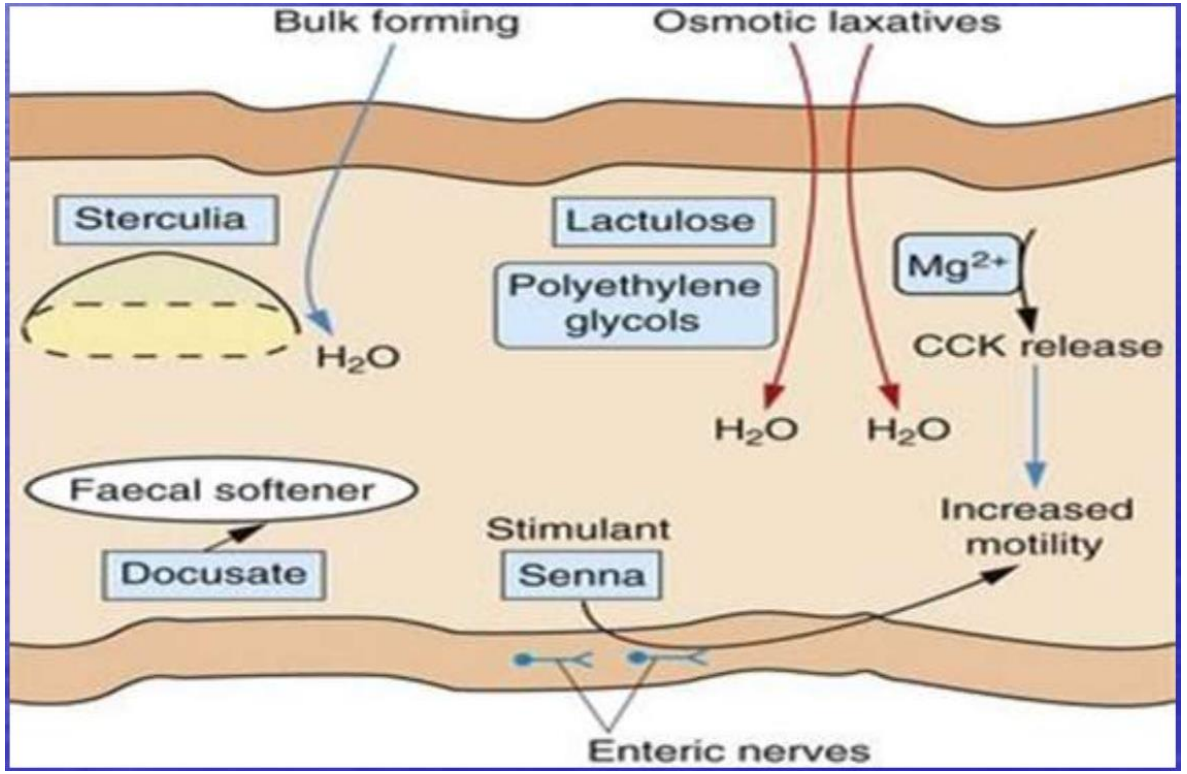
Drug Interactions

- May affect absorption of drugs due to decreased gastric acidity like digoxin and ketoconazole.
- Omeprazole can inhibit metabolism of drugs such as diazepam and phenytoin.
- Rabeprazole and pantoprazole have no significant interaction. Therefore, rabeprazole and pantoprazole are the PPIs of choice if the patient needs to take other drugs as well.

Drugs Affecting GI Motility

Drugs Affecting GI Motility

- Laxative Agents which are used in cases of constipation.
- Antidiarrheal Agents used to treat cases of diarrhea.



Laxatives

Nonpharmacologic Remedies:

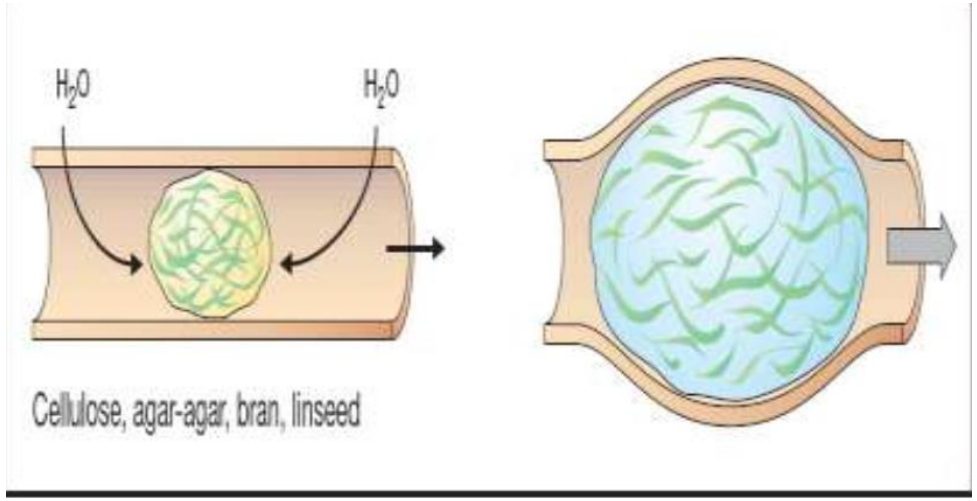
- High fiber diet.
- Adequate fluid intake.
- Regular exercise.
- Responding to nature's call.

We resort to these nonpharmacological remedies to treat constipation before taking laxatives.

Laxatives

Bulk-Forming Laxatives:

- Are indigestible, hydrophilic colloids (gelatinous-like substances) that absorb water, forming a bulky, emollient (softening) gel that distends the colon and promotes peristalsis.
- Can cause bloating and flatus.
- Obtained from Natural Plant Products:
  - Psyllium.
  - Sterculia "Normacol"
  - Methylcellulose.
- Or obtained from Synthetic Fibers:
  - Polycarbophil.



3. Bulk laxatives

Laxatives

Stool Surfactant Agents (Softeners):

- They permit water and lipids to penetrate to soften stool.
- Given orally or rectally.
- Docusate.
- Glycerin suppository are the most famous example of softeners.
- Mineral oil:
  - Clear viscous oil that lubricates fecal material, retarding water absorption from the stool.
  - Used to prevent and treat fecal impaction.
  - Aspiration can cause lipoid pneumonia (Aspiration pneumonia occurs when food or liquid is breathed into the airways or lungs, instead of being swallowed).
  - Can impair absorption of fat-soluble vitamins so vitamin supplements should be given simultaneously.

Laxatives

Osmotic Laxatives (Purgatives):

- Soluble nonabsorbable compounds that result in increased stool liquidity due to an obligate increase in fecal fluid.
- Magnesium oxide (Milk of Magnesia):
  - Can cause hypermagnesemia.
  - Large doses of magnesium citrate and sodium phosphate can cause Purgation: rapid bowel evacuation within1-3 hours. This might cause volume depletion.

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			