H2 Blockers & Proton Pump Inhibitors

Dr.Alaa Alanteet
Dr. Mohammed Almutairi

- Main text
- Male slide
- Female slide
- Important
- Dr, notes
- Extra info

EDITING FILE

Objectives

- Understand the key points of pathophysiology of the peptic ulcer disease
- Enumerate various classes of drugs used in peptic ulcer disease
- Know the characteristic pharmacokinetics, pharmacodynamics and side effects of drugs used in peptic ulcer disease.
- Know the cytoprotective drugs mainly misoprostol and its use in NSAIDs-induced peptic ulcer.
- Identify different antacids that are used to relief pain of peptic ulcer.
- Identify potential adverse drug interactions of anti-ulcer drugs.

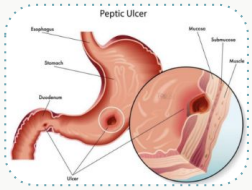
Summery

Dr. Fouda Video

Peptic Ulcer Disease (PUD)

Definition

A localized lesion of the mucous membrane of the stomach (gastric ulcer) or duodenum (duodenal ulcer), typically extending through the muscularis mucosa.



Pathophysiology

◎ Old theory: is imbalance between:
1. Aggressive factors (acid & pepsin)
2. Defensive factors (e.g. prostaglandins, mucus & bicarbonate lyer)

◎ However, nowadays, it seems that H. pylori theory is very important. which is the major etiological factor in peptic ulcer disease (95% in duodenal and 80% in gastric ulcer).

Aggressive factors

◎ **Normal aggressive factors:**
1. Hydrochloric acid (HCL)
2. Pepsin

◎ Destroys gastric and duodenal mucosa

◎ **Aggravating causes** of PUD
1. H. Pylori infection
2. NSAIDs*, Aspirin
3. cigarettes, alcohol
4. impaired regulation of acid-pepsin secretion.

* because NSAIDs will ↓Prostaglandins which are protective factors

* Click here for the slide picture

Defensive factors

★ Could come as SAQ

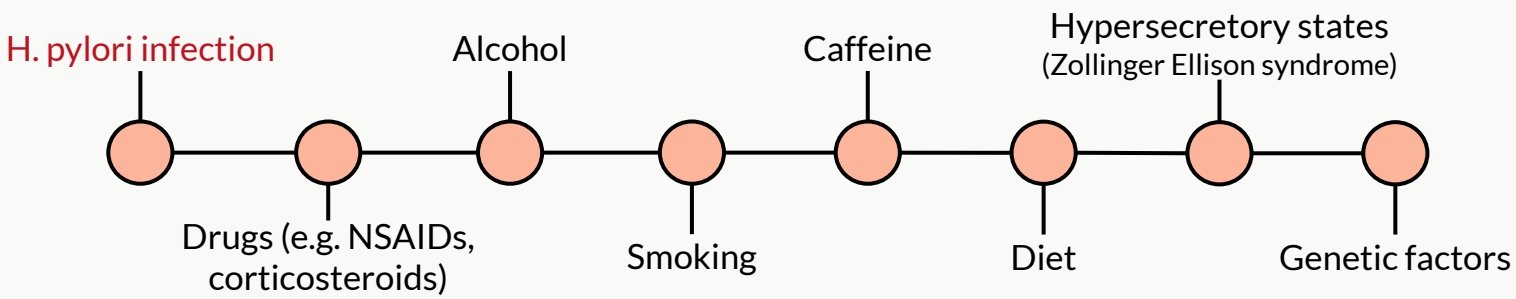
1. **Mucus** and **bicarbonate*** ion secretions protect mucosa

2. **Prostaglandins** (PGE2 & PGI2)
Protect mucosa by:
◦ Inhibiting acid secretion
◦ ↑ mucus & bicarbonate production
◦ Enhancing mucosal blood flow (V.D)

◎ Factors **Impaired the defense:**
Ischemia, shock, delayed gastric emptying, duodenal-gastric reflux.

* If there is an increase in an acidic substance in the body, the body will secrete an alkaline substance to do neutralisation the HCl

Etiology of PU



Peptic Ulcer Disease (PUD)

Etiology of PU cont…

Zollinger Ellison Syndrome

◎ is a disease in which Gastrin-secreting **tumors** (gastrinoma) cause the stomach to produce too much acid, resulting in peptic ulcers. Symptoms include abdominal pain and diarrhea.

◎ Gastrin produces:
- Parietal cell hyperplasia (trophic factor)
- Excessive gastric acid production
- Diarrhea

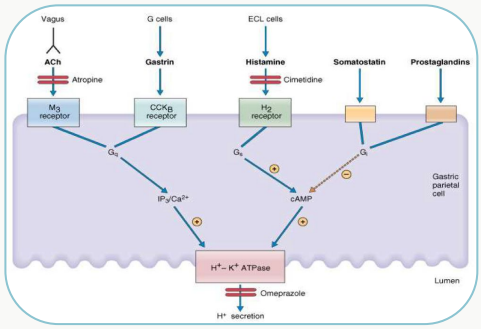
Gastric secretions

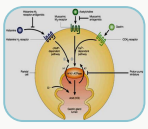
HCl and intrinsic factor (Parietal cells)	Pepsinogens (Chief cells)	Mucus, bicarbonate (mucus-secreting cells)

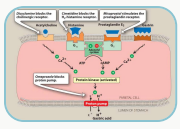
Regulation of gastric secretions

Parietal cells secrete acid in response to:

1. Ach (neurotransmitter): M3 receptors
2. Gastrin (hormone): CCK 2 receptors (cholecystokinin)
3. Histamine (local hormone): H2 receptors
4. Proton pump (H+/ K+ ATPase)







Treatment of P.U

Neutralizing Agents
"create a balance between acid & base"
- antacids (NaHCO3)

Mucosal cytoprotective agents
"used when the problem is in the defensive mechanism not in the HCl it self"
- Prostaglandin analogues

Hyposecretory drugs
↓ gastric acid secretion → Promote healing & relieve pain
"when the cause is ↑ production of HCl itself"
- Proton pump inhibitors
- H2 receptor blockers
- Antimuscarinic drugs

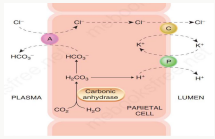
H. pylori infections:
Eradication by Antibiotics & Antacid

The prazoles ! Proton Pump Inhibitors (PPIs)

Drug	Omeprazole	Lansoprazole	Pantoprazole	Rabeprazole

M.O.A

Acts by **irreversible** inhibition of proton pump (H+/ K+ ATPase) that is responsible for final step in gastric acid secretion from the parietal cell (they covalently bind to the pump)



P.K.

- Given orally as enteric coated formulations (unstable in acidic medium in stomach)
- Pro-drugs (converted to the active form after administration in gastric gland -parietal cells-)
- Rapidly absorbed from the intestine then distributed in blood then activated in stomach
- Activated within the acidic medium of parietal cell canaliculi (the site of action)
- At neutral pH, PPIs are inactivated -it require Hcl (acid medium)-
- Should not be combined with H2 blockers -because they inhibit liver enzymes
  - or antacids because they reduce HCl → inactivation of PPIs
- Bioavailability is reduced by food → given one hour before the meal
- Have long duration of action (>12-24h) → once daily dose is sufficient
- Metabolized in the liver by **Cyt-P450** (the cause of drug-drug interactions) → dose reduction is required in severe liver failure

P.D.

- They are the most potent inhibitors of acid secretion available today.
- Produce marked inhibition of basal & meal stimulated-acid secretion (90-98%).
- Reduce pepsin activity.
- Promote mucosal healing & decrease pain.
- Proton pump inhibitors heal ulcers **faster than H2 blockers** and have H. pylori inhibitory properties (antibacterial action)

Uses

- Eradication of H. pylori **(combined with antimicrobial drugs)**.
- Resistant **severe** peptic ulcer (4-8 weeks).
- PPIs are the most effective drugs however, we usually start with H2 blockers first (as PPIs are very **expensive** & reserved for **severe cases only**).
- Gastroesophageal reflux disease (**GERD**) (both Prokinetic and Hyposecretory drugs can be used in GERD)
- Hypersecretory conditions as Zollinger Ellison syndrome & gastrinoma (first choice) (↓HCl production)

ADRs

- CNS: headache
- GIT: diarrhea, abdominal pain
- Achlorhydria (absence of HCl) & Hypergastrinemia (**Explanation**: ↓HCL → ↑gastrin formation by feedback stimulation → accumulation of gastrin → hypergastrinemia)
- Gastric mucosal hyperplasia caused by hypergastrinemia
- Infections: caused by Achorohydra & Hypergastrinemia
  - Increased bacterial flora
  - Increased risk of community-acquired respiratory infections & nosocomial Pneumonia
- Long term use can lead to: (3↓)
  - ↓ Production of intrinsic factors from stomach wall → Vitamin B12 deficiency
  - ↓ Magnesium → Hypomagnesemia
  - ↓ Calcium → Osteoporosis -for Ca^{++} to be absorbed, it must dissolve in acidic medium-

◎Precaution: do not combine Omeprazole (CYP2C19 inhibitor) and clopidogrel (antiplatelet), because (CYP2C19) is required for activation of clopidogrel.

The tidines!

H2 Receptor Blockers

Drugs	Cimetidine Most ADRs	Ranitidine	Famotidine Most potent	Nizatidine Greatest Bioavailability
M.O.A	They ★ **reversibly and competitively** block **H2** receptors on the parietal cells			
P.K	◦ Good oral absorption. ◦ Given **before** meals. ★ **Famotidine** is the **most potent** drug. ◦ Exposed to first pass metabolism, **except nizatidine** which has the greatest bioavailability ◦ Duration of action (4-12 h). ◦ Metabolized by liver. ◦ Excreted mainly in urine.			
Uses	◦ **GERD** (heartburn / dyspepsia). ◦ **Acute ulcer healing in moderate cases** (if severe → PPI) - Duodenal ulcer (6-8 weeks). - Benign gastric ulcer (8-12 weeks). ◦ **Prevention of bleeding** from **stress-related gastritis**. ◦ **Preanesthetic** medication (to prevent aspiration pneumonitis). ◦ Post–ulcer healing maintenance therapy to prevent relapse.			
P.D	◦ ↓ Basal and food stimulated-acid secretion. ◦ **Block 90% of nocturnal acid secretion** (which depend largely on histamine) & 60-70% of total 24hr acid secretion → better to be given **before night sleep**. ◦ ↓ pepsin activity. ◦ Promote mucosal healing & decrease pain.			
ADRs	◦ **GIT** disturbance: Nausea & vomiting. ◦ **CNS** effects: Headache - confusion (in elderly, hepatic dysfunction and renal dysfunction) ◦ **Bradycardia and hypotension in rapid I.V.** (so must inject slowly) ◦ **Only Cimetidine:** all the below is in cimetidine 1. CYT-P450 inhibition → ↓ metabolism of **warfarin, phenytoin, benzodiazepines** 2. **Endocrine effects**: - **Galactorrhea** (Hyperprolactinemia) - **Antiandrogenic actions** (gynecomastia–impotence) due to inhibition of dihydrotestosterone binding to androgen Receptors. "★Cimetidine" ◎**Precaution:** dose **reduction** in severe **renal** or **hepatic** failure and **elderly.**			

H2 receptor blockers	Cimetidine	Ranitidine	Famotidine	Nizatidine
Efficacy	+++	+++	+++	+++
Potency	+	++	**+++**	++
Dose (Don't memorize)	400 mg bid	150 mg bid	20 mg bid	150 mg bid
CYT-P450	**++**	-	-	-
Antiandrogenic	**++**	-	-	-
Drug interactions	**Many**	No	No	No

Prostaglandin Analogues

Drug	Misoprostol
MOA	◦ Prostaglandin analogues (**PGE1**). (analogue means similar) ◦ ↓HCL secretion (because it ↓CAMP) ◦ ↑ **Protective** measures (↑mucous / bicarbonate & gastric mucosal blood flow).
P.K	Orally, must be taken 3-4 times/day.
Uses	◦ Used for NSAIDs - induced peptic ulcer (NSAIDs ↓PG) ◦ Labor induction
ADRs	◦ Abdominal cramps; diarrhea -Dr. Fouda: anything ↓HCl will cause diarrhea- ★ Uterine contraction (dysmenorrhea or abortion) (Because it is an abortifacient # in pregnancy) ★ Vaginal bleeding.

Antacids (Inorganic Salts)

Drug	NaHCO3 Sodium bicarbonate	CaCO3 Calcium carbonate	Al(OH)3* Aluminum hydroxide	Mg(OH)2* Magnesium hydroxide
MOA	Acts by direct chemical neutralization of HCl (because they alkaline) & ↓ pepsin activity.			
Uses	◦ **Not** considered a treatment of peptic ulcer. ◦ Used to **relieve pain** of peptic ulcer & for dyspepsia (**temporary**, no effect on secretions) ◦ All antacids ↓absorption of some drugs (↓HCl) as tetracycline, fluoroquinolones, iron			
ADRs	◦ Effective, but systemic alkalosis may occur. ★ # in CVD patients Na causes salt & water retention→ hypertension	◦ Hypercalcemia → Milk-alkali syndrome** ◦ ↓absorption of tetracycline ◦ Renal failure	★ Constipation ◦ Hypophosphatemia (weakness, malaise, anorexia) ◦ Seizure in renal patients	★ Diarrhea ◦ Hypotension ◦ Cardiac arrest

* Aluminum cause constipation while Magnesium cause diarrhea so they are mixed in 1 tablet to cancel out each other's ADRs.

**Patient with PU usually administer large amount of milk & antacid to relieve symptoms of hyperacidity.
- excess milk → hypercalcemia
- excess antacid → alkalosis

Summary from slides

★ Test for H. pylori prior to beginning therapy.
◦ Acid-reducing medications are prescribed in case of PUD **without H pylori infections**
◦ Acid-reducing medications for PUD include:
- H2 receptor blockers. "ارخص"
- PPIs should be used for acute therapy only if H2RAs fail or cannot be used, or as part of treatment for H. pylori. "if not improved"

◦ Complete H. pylori eradication is required to prevent relapse.
◦ **PUD with H pylori infections** can be treated with triple therapy or quadruple therapy

MCQ

1. Which of the following is an adverse effect associated with long-term use of proton pump inhibitors?			
A. Diarrhea	B. Abdominal pain	C. Hypomagnesemia	D. Headache
2. Which H2 receptor blocker has the greatest bioavailability?			
A. Cimetidine	B. Ranitidine	C. Famotidine	D. Nizatidine
3. What is the mechanism of action of proton pump inhibitors (PPIs)?			
A. Reversible inhibition of H2 receptors	B. reversible inhibition of proton pump	C. Irreversible inhibition of proton pump	D. Inhibition of prostaglandin synthesis
4. Which of the following is considered a aggressive factor in peptic ulcer disease?			
A. Hydrochloric acid (HCl)	B. Prostaglandins	C. Mucus and bicarbonate	D. Blood flow
5. Which of the following drugs is commonly used as a mucosal cytoprotective agent in peptic ulcer disease?			
A. Omeprazole	B. Misoprostol	C. Ranitidine	D. Pantoprazole
6. Which of the following is a potential adverse effect associated with H2 receptor blockers?			
A. Hypomagnesemia	B. Headache	C. Diarrhea	D. Thrombocytopenia
7. What is the main mechanism of action of antacids in relieving pain in peptic ulcer disease?			
A. Inhibition of acid secretion	B. Neutralization of gastric acid	C. Enhancement of mucus production	D. Promotion of mucosal healing

1:C ,2:D ,3:C ,4:A ,5:B ,6:B ,7:B

SAQ

01

Mr. Johnson, a 55-year-old male, presents to the clinic with complaints of recurrent abdominal pain & discomfort. He reports a burning sensation in his stomach, especially after meals. He has a history of smoking and occasional alcohol consumption. Physical examination reveals epigastric tenderness.

1. What is the most likely diagnosis of Mr. Johnson's symptoms?
2. Name 2 aggressive factors that contribute to the development of peptic ulcer disease?
3. Which defensive factors protect the gastric mucosa from damage?
4. What is the major causative factor in peptic ulcer disease, particularly in duodenal ulcers?
5. How do NSAIDs contribute to the development of peptic ulcers?
6. Which class of drugs is known to inhibit acid secretion and promote mucosal healing in peptic ulcer disease?
7. What are the potential adverse effects of question 6?

02

Ms. Rodriguez, a 40-year-old female, presents to the clinic with abdominal pain and black, tarry stools. She has a medical history of chronic NSAID use for her chronic arthritis. On examination, she appears pale and has a rapid heart rate. Abdominal examination reveals epigastric tenderness and a positive stool guaiac test.

1. What is the most likely diagnosis for Ms. Rodriguez's symptoms?
2. Explain the pathophysiology of the condition mentioned in question 1.
3. How do NSAIDs contribute to the development of the condition?
4. Name two defensive factors that protect the gastric mucosa.
5. Which drug class is commonly used for treating the condition mentioned in question 1?
6. Describe the mechanism of action of the drug in question 5?
7. What are the potential adverse effects of histamine H2 receptor blockers commonly used in the treatment of the condition?

Case Scenario 1 Answers:

1. peptic ulcer disease.
2. hydrochloric acid (HCl) and pepsin.
3. mucus and bicarbonate ion secretions.
4. Helicobacter pylori (H. pylori) infection.
5. by ↓ production of prostaglandins, which are protective factors for the gastric mucosa.
6. Proton pump inhibitors (PPIs)
7. headache, diarrhea, abdominal pain, achlorhydria, hypergastrinemia, gastric mucosal hyperplasia, ↑ risk of infections, ↓ Vit B12, Mg, and Ca.

Case Scenario 2 Answers:

1. gastrointestinal bleeding, possibly due to a peptic ulcer.
2. imbalance between aggressive factors (such as HCl & pepsin) and defensive factors (including mucus & bicarbonate) in the gastric mucosa → erosion & ulceration.
3. by ↓ production of prostaglandins, which are protective factors for the gastric mucosa.
4. mucus and bicarbonate secretions.
5. prostaglandins analogues (Misoprostol)
6. Prostaglandin analogues (**PGE1**), ↓HCL secretion,↑ **Protective** measures (↑mucous / bicarbonate & gastric mucosal blood flow).
7. Abdominal cramps; diarrhea, Uterine contraction (dysmenorrhea or abortion), Vaginal bleeding.

Team Leaders

Muhnnad Al-Otaibi

Reema Almotairi

Sarah Alajaji

Team members

Maryam Alghannam

Aroub Almahmoud

Layan Sulaiman

Aishah Boureggah

Areej Alquarini

Lama Alotaibi

Jana alshiban

Layan Alruwaili

Sara Alharbi

Fatimah Alghamdi

Alanoud Abdullah

Nourah alarifi

Renad Alotaibi

Wafa Alakeel

Wasan Alanazi

Ayedh Alqantash

Nazmi A Alqutub

Yousef badgesh

Mohammed Alqutub

Fahad Aldhafian

Special thanks to Norah Almania for the amazing logo