Revised & Approved

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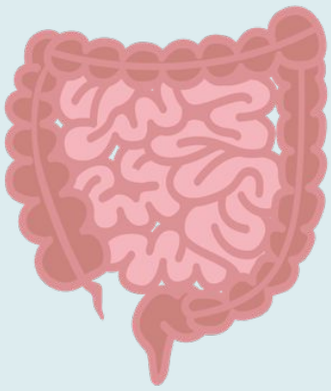
Pharmacology 439

MED439



Gastrointestinal Block

Pharmacology Team 439

Helpful video

Color index:

Main Text

Important

Dr's Notes

Female Slides

Male Slides

Extra

H_2 Receptors And Proton Pump Inhibitors

Objectives:

1-Understand the key points of pathophysiology of the peptic ulcer disease

2-Enumerate various classes of drugs used in peptic ulcer disease

3-Know the characteristic pharmacokinetics, pharmacodynamics and side effects of drugs used in peptic ulcer disease.

4-Know the cytoprotective drugs mainly misoprostol and its use in NSAIDs- induced peptic ulcer.

5-Identify different antacids that are used to relief pain of peptic ulcer.

6-Identify potential adverse drug interactions of anti-ulcer drugs.

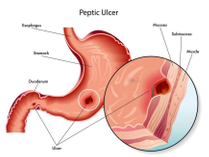
Editing file | Summary

Peptic Ulcer Disease (PUD)

Peptic Ulcer Disease (PUD)

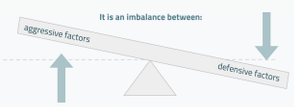
A localized lesion of the mucous membrane of the stomach **(gastric ulcer)** or duodenum **(duodenal ulcer)**, typically extending through the muscularis mucosa.

If not treated it could lead to:
superinfections, bleeding, perforation, cancer, and malnutrition



Pathophysiology of PUD

It is an imbalance between:



1. Aggressive factors **(acid & pepsin)**
2. Defensive factors **(e.g. prostaglandins, mucus & bicarbonate layer)**.

However, nowadays, it seems that **H. pylori theory** is very important.

1- Aggressive factors*

1- Hydrochloric acid (HCl)
2- Pepsin

What do they do?

destroy gastric and duodenal mucosa

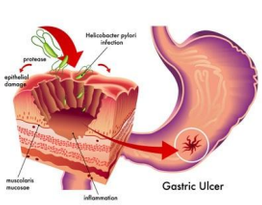
2- Defensive factors*

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

2- Prostaglandins (PGE_2 & PGI_2), **protect mucosa** by:

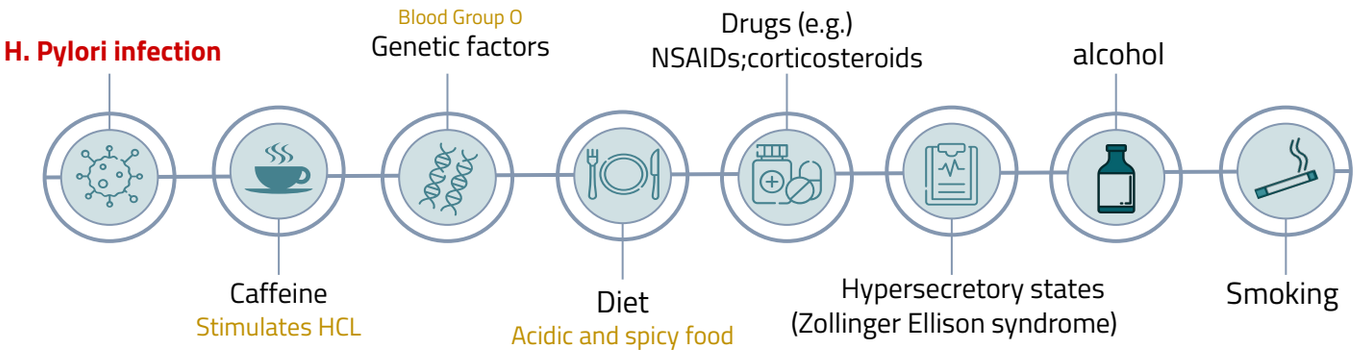
- Inhibiting acid secretion.
- Increasing mucus and bicarbonate production
- Enhancing mucosal blood flow.

Helicobacter pylori is the major etiological factor in peptic ulcer disease (95% in duodenal and 80% in gastric ulcer).



*In treatment of Peptic ulcers, We try to decrease aggressive factors and support defensive factors

Etiology of PUD



Zollinger Ellison syndrome:

Is a disease in which Gastrin -secreting **tumors** 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)
- diarrhea
- Excessive gastric acid production

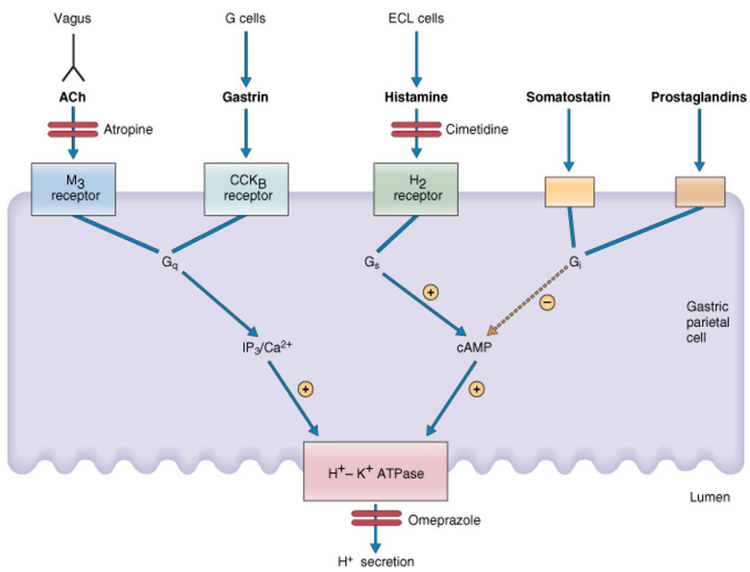
Gastric secretions

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): M_3 receptors
2. Histamine (local hormone): H_2 receptors
3. Gastrin(hormone): CCK2 receptors (cholecystokinin)
4. Proton pump most effective (H^+/ K^+ ATPase)



Treatment Of Peptic Ulcer:

1

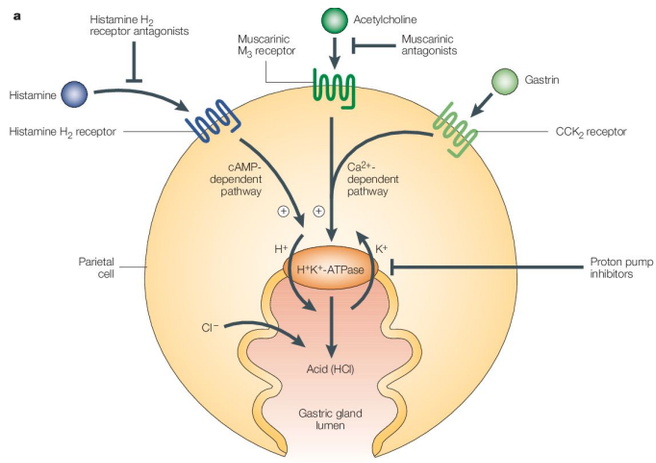
Eradication of H. pylori infections Refer to micro for more details
(Combination of Metronidazole/Clarithromycin and PPIs)

2

Mucosal cytoprotective[1] Agents

Prostaglandin analogues e.g. Misoprostol

1: due to mucus bicarb secretion



3

Neutralizing agents

antacids e.g. Sodium Bicarbonate ($NaHCO_3$)

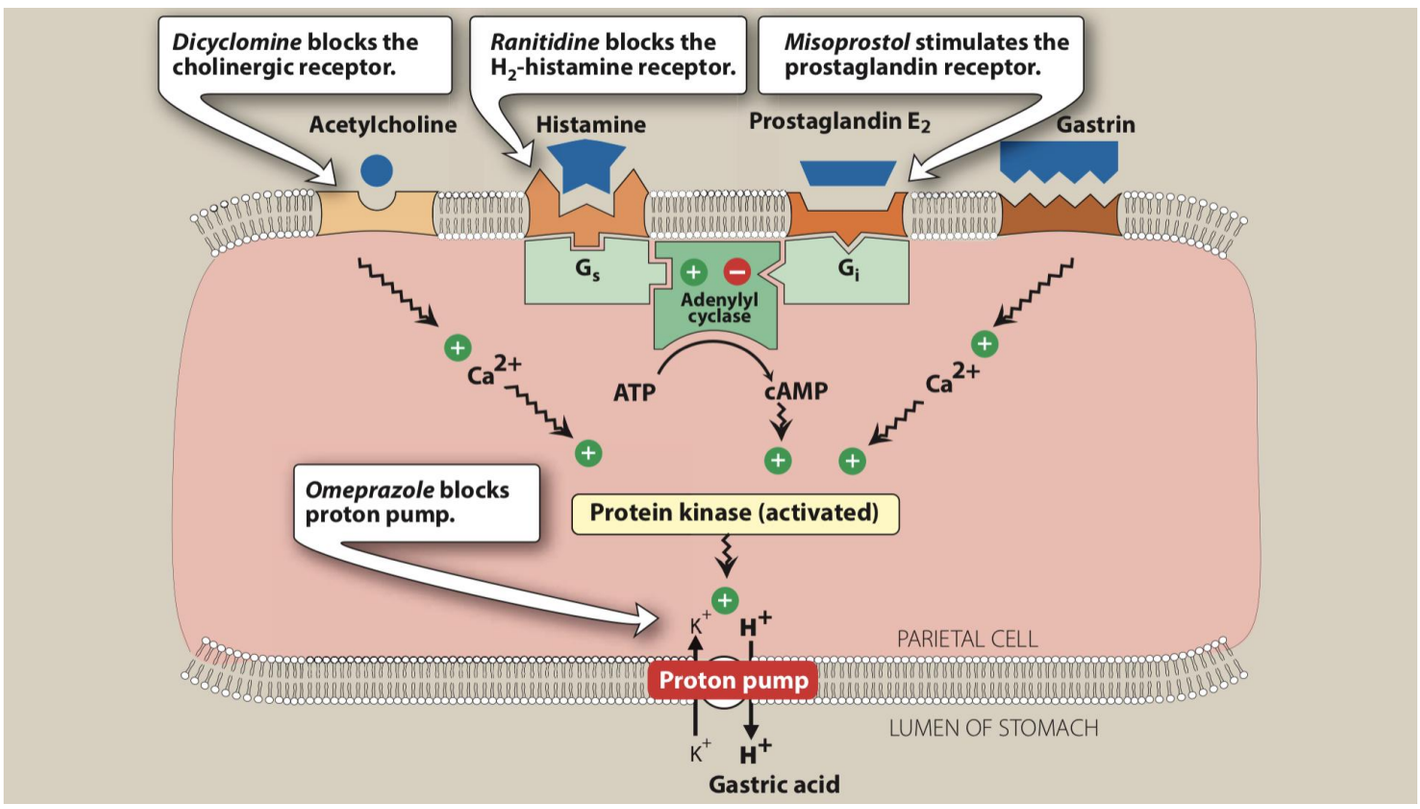
4

Gastric Hyposecretory drugs:

Proton pump inhibitors, H_2 receptor blockers, Antimuscarinic drugs

Hyposecretory drugs **decrease gastric acid secretion** → Promote healing & relieve pain. **Include:**

- Proton pump inhibitors (PPI) most effective because it's the final step
- H_2 receptor blockers
- Antimuscarinic drug (theoretically should work but in reality not very effective)

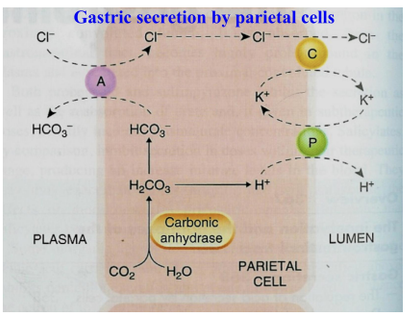


Proton Pump Inhibitors (PPIs)

Drug	Omeprazole Cheaper	Lansoprazole	Pantoprazole More expensive but better	Raprazole

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.
- Rapidly absorbed from the intestine. Note that it is absorbed in intestine, distributed in blood, then it is activated in stomach
- Activated within the acidic medium of parietal cell canaliculi.
- At neutral pH, PPIs are inactivated.
- Should not be combined with H_2 blockers or antacids. They require an acidic medium to be activated
- 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.
- 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 (fasting) & meal stimulated-acid secretion (90-98%).
- Reduce pepsin activity. because it requires HCL for activation
- Promote mucosal healing & decrease pain.
- Proton pump inhibitors heal ulcers faster than H_2 blockers and have H. pylori inhibitory properties.

Uses

- PPIs are the most effective drugs. However, we usually start with H2 blockers first (as PPIs are preserved for severe cases only & are very expensive).
- Eradication of H. pylori (combined with antimicrobial drugs).
- Resistant **severe** peptic ulcer (4-8 weeks).
- Reflux Esophagitis/Gastroesophageal reflux disease (GERD).
- ★ Hypersecretory conditions as **Zollinger Ellison syndrome and gastrinoma** (First choice).

ADRs

- CNS: headache
- GIT: diarrhea, abdominal pain

Short term use is safe but long may lead to:

- ★ Achlorhydria (low HCl) & Hypergastrinemia (increased serum gastrin level)
- Gastric mucosal hyperplasia. To avoid this, It's recommended that you stop taking the drug every few weeks
- **Infections**:
  - Increased bacterial flora due to Achlorhydria
  - Increased risk of community-acquired respiratory infections & nosocomial Pneumonia.
  - increased risk of enteric infections including C. Difficile (Causing pseudomembranous colitis) and bacterial gastroenteritis.

Long term use can lead to:

- Decreased B_{12}, Iron, calcium absorption
- Hypomagnesemia
- Decrease calcium → Osteoporosis → increased risk of hip fractures

Precaution

- Do not combine Omeprazole (CYP2C19 inhibitor) and clopidogrel (antiplatelet), because (CYP2C19) is required for activation of clopidogrel.

H_2 receptor blockers

Drug	Cimetidine Most toxic	Ranitidine	Famotidine Most potent	Nizatidine Most bioavailable
M.O.A	• They **reversibly** and competitively block H_2 receptors on the parietal cells.			
P.k	• Good oral absorption • Given before meals to control acid secretion after meals • Famotidine is the **most potent** drug. • Exposed to first pass metabolism except nizatidine, which has the greatest bioavailability. • Excreted mainly in urine • Duration of action (4-12 h). • Metabolized by liver. • Given twice or 3 times a day			
Action	• Reduce basal and food stimulated-acid secretion. ★ Block 90% of nocturnal acid secretion (which depend largely on histamine) & 60-70% of total 24 hr acid secretion. Therefore,it is better to be given before night sleep • Reduce pepsin activity. • Promote mucosal healing & decrease pain.			

Uses
Don't use them for Z-E Syndrome
	• GERD (heartburn/ dyspepsia).
	• Acute ulcer healing in moderate cases as PPIs are expensive & preserved for severe cases.
	  ○ 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			

ADRs	Serious adverse effects are RARE
	• GIT disturbance: Nausea & vomiting.
	• CNS effects: Headache - confusion (in elderly, hepatic dysfunction, renal dysfunction).
	• Bradycardia and hypotension (if given rapid I.V.)
	• **Only Cimetidine:** CYT-P450 inhibition **decrease** metabolism of warfarin, phenytoin, benzodiazepines.
	• Endocrine effects **(Only cimetidine)**
	  ○ **Galactorrhea** (Hyperprolactinemia)
	  ○ **Antiandrogenic actions** (gynecomastia –impotence) due to inhibition of dihydrotestosterone binding to androgen Receptors.			

Precaution	• Dose reduction in severe renal or hepatic failure and elderly.			

H_2 receptor blockers Click for full table (what's here is enough)	Cimetidine	Ranitidine	Famotidine Most potent	Nizatidine
Efficacy	+++	+++	+++	+++
Potency inverse relationship with dose	+	++	+++	++
Dose not imp	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
M.O.A	• Prostaglandin analogues (PGE_1) • ↓HCL secretion • ↑Protective measures (↑ mucous/bicarbonate & gastric mucosal blood flow)
P.k	• Orally, must be taken 3-4 times/day.
Uses	★ Drug of choice for **NSAIDs - induced peptic ulcer** (NSAIDs ↓ PG) e.g arthritis patient • labor induction
ADRs	• Abdominal cramps; diarrhea. Due to contractions • Uterine contraction (dysmenorrhea or abortion). Contraindicated for pregnant • Vaginal bleeding

Antacids (Inorganic Salts)

Drug	$NaHCO_3$ Sodium bicarbonate	$CaCO_3$ Calcium carbonate	$Al(OH)_3$* Aluminum hydroxide	$Mg(OH)_2$* Magnesium hydroxide
M.O.A	• Acts by direct chemical **neutralization of HCL** and decrease pepsin activity.			
Uses	• Used to relieve pain (temporary, no effect on secretion) of peptic ulcer & for dyspepsia. But it's NOT recommended for PUD • All antacids ↓ absorption of some drugs as tetracycline, fluoroquinolones, iron. • Only used for **very short term** management, rebound acidity may occur with long term due to compensation			
ADRs	- Effective, but Systemic alkalosis may occur - Contraindicated In CVS patients due to water retention	- Milk-alkali syndrome (Alkalosis) - Hypercalcemia - Renal failure - ↓ absorption of tetracycline.	Eat with Aluminum CHOPSticks - **C**onstipation* Aluminum = Minimum amount of feces - **H**ypophosphatemia (**P**roximal weakness, malaise, anorexia) - **O**steodystrophy - **S**eizures. (renal patients)	- Osmotic Diarrhea* Mg2 = Must go 2 the bathroom - Cardiac arrest - Hypotension

* Aluminum & Magnesium hydroxide are available as 1 tablet to compensate for/cancel out each other's ADRs

Summary from Dr 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:
  - H_2 receptor blockers
  - PPIs should be used for acute therapy only if H_2RAs fail or cannot be used, or as part of treatment for H. pylori.
- Complete H. pylori eradication is required to prevent relapse.
- **PUD with H pylori infections can be treated with** triple therapy or quadruple therapy

Summary

Drug	M.O.A	Uses	ADRs	Precaution
Gastric hyposecretory drugs				
Proton pump inhibitors (MOST potent & Have H.Pylori INHIBITORY effect)				
Omeprazole **Lansoprazole** **Pantoprazole** **Raprazole**	Irreversible inhibition of proton pump (H^+/K^+ ATPase)	- Eradication of H. pylori w/ antibiotics - Zollinger Ellison syndrome and gastrinoma (first choice) - Resistant severe peptic ulcer - GERD	**Long term use:** -Achlorhydria & Hypergastrinemia -Gastric mucosal hyperplasia -Infection - Vitamin B12 deficiency - Hypomagnesemia -Osteoporosis - ↓iron absorption	Omeprazole (CYT2c19 inhibitor) should not be combined with clopidogrel
H_2 receptor blockers				
Cimetidine **Rantidine** **Famotidine** **Nizatidine**	They reversibly and competitively block H_2 receptors on the parietal cells. Block 90% of nocturnal acid secretion, given before night sleep	●GERD (heartburn/ dyspepsia). ● Acute ulcer healing in moderate cases ● Preanesthetic medication (to prevent aspiration pneumonitis). ● Post–ulcer healing maintenance therapy	- Headache, confusion (in elderly, hepatic\renal dysfunction) - Bradycardia & hypotension **Only cimetidine:** - CYT-P450 inhibition (↓Warfarin, phenytoin, Benzodiazepine) - Galactorrhea (hyperprolactinemia) - Antiandrogenic actions (gynecomastia, impotence)	Dose reduction in severe renal or hepatic failure and elderly..
Mucosal cytoprotective agents				
Prostaglandin analogues (PGE_1)				
Misoprostol	- ↓HCL production - ↑ protective measures (↑mucous/bicarbonate & gastric mucosal blood flow	● Drug of choice for NSAIDs - induced peptic ulcer, e.g arthritis ● labor induction	● Abdominal cramps; diarrhea. ● **Uterine contraction** (dysmenorrhea or abortion). ● **Vaginal bleeding**	—
Neutralizing agents				
Antacids (Inorganic salts)				
NaHCO3	● Acts by direct chemical neutralization of HCL and decrease pepsin activity	● Relieve pain of peptic ulcer & dyspepsia	- Systemic alkalosis - C.I=CVS patients	—
CaCO3			- Milk-alkali syndrome - Hypercalcemia - Renal failure -↓ absorption of tetracycline.	
Al(OH)3			- Constipation - Hypophosphatemia - Seizures.	
Mg(OH)2			-Diarrhea - Cardiac arrest, hypotension	

MCQs

Q1: Dr's: 39-year-old female presents to your clinic complaining of epigastric pain. You decide to do an endoscopy and find a peptic ulcer. Which one of the following is NOT a good choice for management for this patient			
A- Famotidine	B- Misoprostol	C- Calcium carbonate	D- Pantoprazole
Q2: 27-year-old pregnant woman presented to your office with acute abdominal burning pain in the epigastric region. She had a growing digestive discomfort and low-grade pain for months. Which one of the following drugs is contraindicated in her case?			
A- Cimetidine	B- Famotidine	C- Lansoprazole	D- Misoprostol
Q3: 51-year-old patient suffering from epigastric pain and burning sensation that disturbs his sleep at night, he's been taking an antacid that he can't remember its name, He came due to osmotic diarrhea, which of the following could have triggered it?			
A- Magnesium hydroxide	B- Aluminum hydroxide	C- Calcium carbonate	D- Sodium bicarbonate
Q4: A 60-year-old man suffering from recurrent heartburn routinely took large quantities of different antacid preparations. Which of the following antacids had the highest risk of metabolic alkalosis in this patient?			
A- Magnesium hydroxide	B- Aluminum hydroxide	C- Calcium carbonate	D- Sodium bicarbonate
Q5: An elderly woman with a recent history of myocardial infarction is seeking a medication to help treat her occasional heartburn. She is currently taking several medications, including aspirin, clopidogrel, simvastatin, metoprolol, and lisinopril. Which drug should be avoided in this patient?			
A- Omeprazole	B- Famotidine	C- Ranitidine	D- Pantoprazole
Q6: A 54 year-old patient diagnosed with Zollinger-Ellison syndrome, what drug should his physician prescribe?			
A- Famotidine	B-Omeprazole	C-Misoprostol	D-Sodium bicarbonate
Q7: A 37 year-old lady was suffering from vomiting due to GERD. She was prescribed a drug for her vomiting. She came back to the hospital complaining of milky secretions. Which of the following drugs is most likely to cause this?			
A- Omeprazole	B- Misoprostol	C- Cimetidine	D- Ranitidine
Q8: 56-year-old patient who has been taking NSAIDs for a long time developed peptic ulcer, what's the drug of choice in his condition?			
A- Omeprazole	B- Misoprostol	C- Cimetidine	D- Ranitidine
Q9: 30-years-old female with a history of deep vein thrombosis was diagnosed with peptic ulcer, and she was treated successfully. Her doctor wants to prescribe a medication to prevent relapse of her ulcer. What is the best choice?			
A- Cimetidine	B- Famotidine	C- Lansoprazole	D- Misoprostol

1	2	3	4	5	6	7	8	9
C	D	A	D	A	B	C	B	B

SAQ

Case: A 61-year-old woman was referred to a Gastroenterology Clinic from primary care provider due to consistent discomfort and significant weight loss. She presented with a 2-month history of burning pain in the epigastric abdomen and chest which radiated toward her back.

Q1) Mention three drug classes that can be used to treat this patient.

A-
B-
C-

Q2) Mention the MOA & give an example of a drug name from classes A,B, and C.

A-
B-
C-

Q3) Mention 2 side effects for each class

A-
B-
C-

Answers

A1)

A- Proton pump inhibitors
B- H2 receptor blockers
C- Prostaglandin analogues

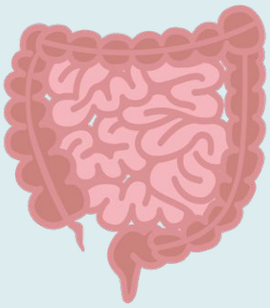
A2)

A- Irreversible inhibition of proton pump (H+/K+ ATPase) > **Omeprazole**
B- Reversible and competitive block H2 receptors on the parietal cells. > **Famotidine**
C- ↓HCL production ↑ protective measures > **Misoprostol**

A3)

A- Achlorhydria, hypergastrinemia, and infections.
B- Nausea, vomiting, headache, and confusion
C-Vaginal bleeding, uterine contraction, and diarrhea

Feedback Form



Gastrointestinal Block

Pharmacology Team 439

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