

## H2 blockers and proton pump inhibitors

### 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 (**proton pump inhibitors, and H2 receptor blockers**).
- 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.

Editing File

Color index: **Important** **Note** **Extra**

# Mind Map

## 1) Hyposecretory drugs

Proton pump inhibitors

Omeprazole -Lansoprazole -Pantoprazole- Rabeprazole

H<sub>2</sub> Receptor Blocker

Cimetidine -Ranitidine Famotidine -Nizatidine

Antimuscarinic

Pirenzepine

## 2) Mucosal cytoprotective agents

Prostaglandin Analogue

Misoprostol

## 3) Neutralizing agents

Antacids

Inorganic salts: NaHCO<sub>3</sub> - CaCO<sub>3</sub>  
Al(OH)<sub>3</sub> - Mg(OH)<sub>2</sub>

Mnemonics:

طيب خذوا رنا؟ لا نسوا رنا.. أمي والبنات برا

برا = prazole

أمي = Omeprazole

البنات = Pantoprazole

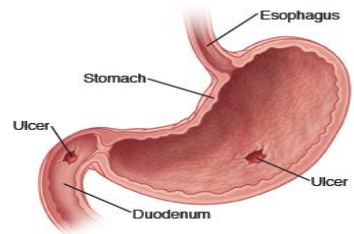
لا نسوا = Lansoprazole

رنا = Rabeprazole

Special thank for Dimah Alaraifi 

# 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.



## Pathophysiology

It is an imbalance between aggressive factors (**acid & pepsin**) and defensive factors (e.g. **prostaglandins** **Cox2 inhibitors**, **mucus & bicarbonate layer**).

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

Girl's Slides Only

### A. Aggressive factors

1. Hydrochloric acid and pepsin destroy gastric and duodenal mucosa.

### A. Defensive factors

1. Mucus and bicarbonate ion secretions protect mucosa
2. Prostaglandins (PGE2 & PGI2) protect mucosa by:
  - Inhibiting acid secretion.
  - Increasing mucus and bicarbonate production.
  - Enhancing mucosal blood flow.
  - **PG increase cell turnover**

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

## Etiology

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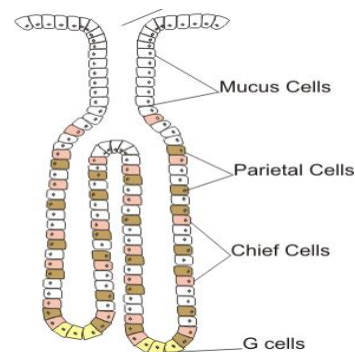
- ★ *H. Pylori* infection
- ★ Drugs (e.g.) NSAIDs; corticosteroids **they decrease PG**
- ★ Alcohol
- ★ Smoking
- ★ Caffeine **increase gastric acid secretion**
- ★ Genetic factors **blood group O are more susceptible**
- ★ Diet
- ★ Hypersecretory states (Zollinger Ellison syndrome) **tumor of gastrin cells**

# Treatment Of Peptic Ulcer

1. Eradication of H. pylori infections (combination of metronidazole/ clarithromycin and PPIs) by antibiotics. After we exclude H.pylori infection we treat with the other drugs
1. Hyposecretory drugs:
  - Proton pump inhibitors
  - H2 receptor blockers
  - Antimuscarinic drugs
1. Mucosal cytoprotective agents: additive therapy
  - Prostaglandin analogues
4. Neutralizing agents (antacids)

# Gastric secretions

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



# Regulation of gastric secretions

Parietal cells secrete acid in response to:

1. Ach (neurotransmitter): M3 receptors
2. Gastrin (hormone): CCK2 receptors(cholecystokinin)

**3. Histamine (local hormone): H2 receptors**

**4. Proton pump (H<sup>+</sup>/ K<sup>+</sup> ATPase)**

**Most Important**

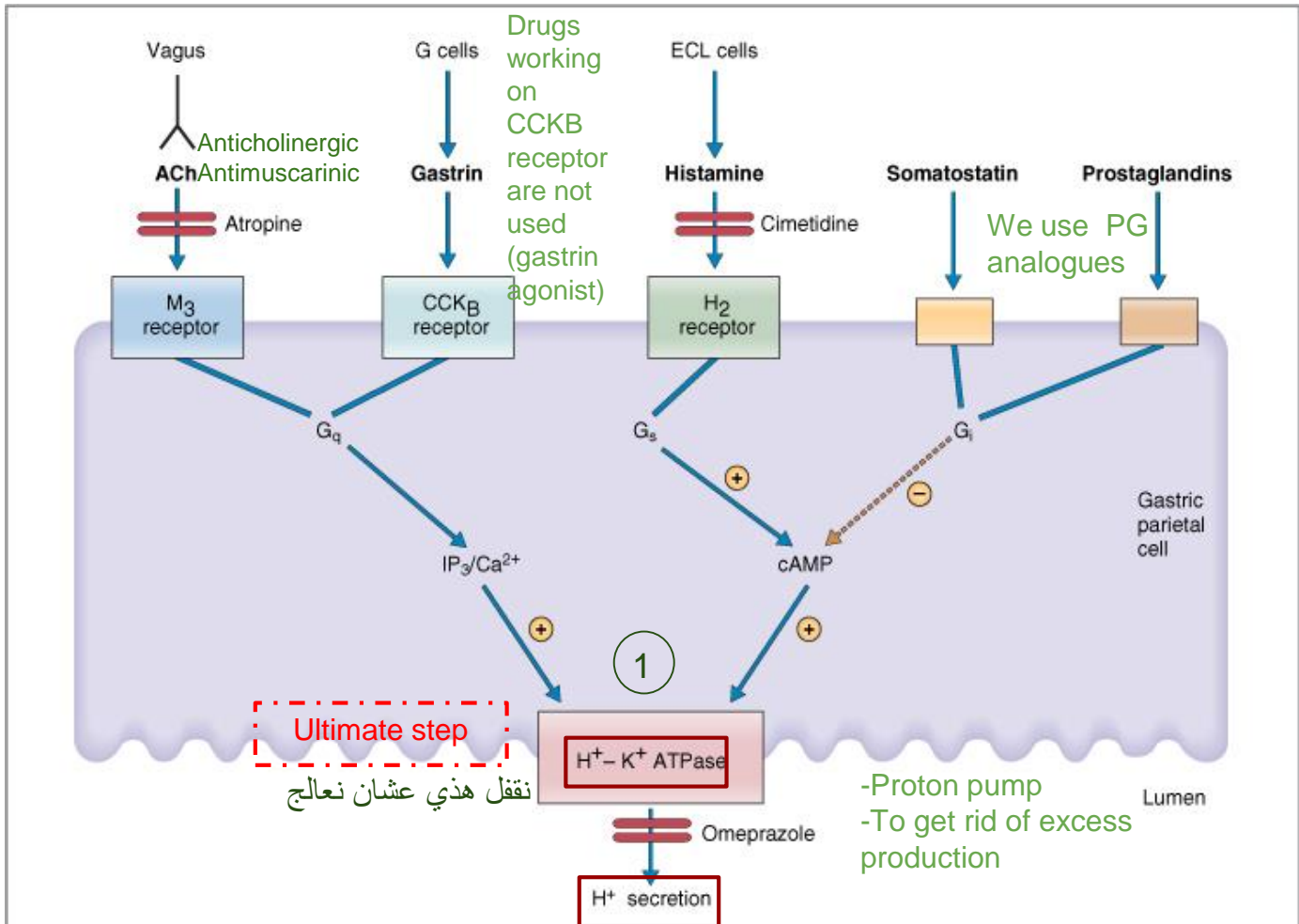
# Gastric hyposecretory drugs

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

- Proton pump inhibitors
- H2 receptor blockers
- Antimuscarinic drugs

الصورة موجودة في سلايدز البنات فقط ، لكن بسلايدز العيال فيه صورة غير هذي ، وكلا الصورتين يتضمنون نفس الفكرة .  
تم الاعتماد على هذي الصورة لأن بروف حنان شرحت عليها .

## Very IMP Pictures



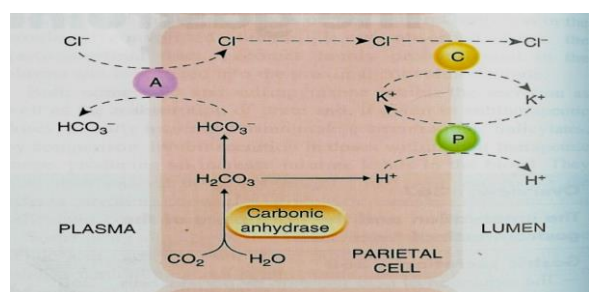
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Note: the term antihistamine means H1 blockers (for allergies). Here we are using H2 blockers not H1, so don't list antihistamines as a therapeutic agent for peptic ulcer .

# Proton Pump Inhibitors (PPIs)

Drug	Omeprazole	Lansoprazole	Pantoprazole	Raprazole
M.O.A	Acts by <b>irreversible</b> (so long effect) <b>inhibition of proton pump (H<sup>+</sup>/ K<sup>+</sup> ATPase)</b> that is responsible for final step in gastric acid secretion from the parietal cell (they covalently bind to the pump). <b>1 tablet - 24 hrs</b>			
P.D	<ul style="list-style-type: none"> <li>● They are the <b>most potent inhibitors of acid secretion</b> available today.</li> <li>● Produce marked inhibition of basal &amp; meal stimulated-acid secretion(90-98%).</li> <li>● <b>Reduce pepsin activity.</b></li> <li>● Promote mucosal healing &amp; decrease pain.</li> <li>● <b>Proton pump inhibitors heal ulcers faster than H<sub>2</sub>blockers, and have H. pylori inhibitory properties. (That's why we use it in the triple therapy)</b></li> </ul>			
P.K	<ul style="list-style-type: none"> <li>● Given orally , are pro-drugs. Absorbed first in the intestine then goes back to the stomach</li> <li>● Given as <b>enteric coated</b> to prevent the stomach from breaking it down and reach the <b>intestine</b> formulations (<b>unstable in acidic medium in stomach</b>).</li> <li>● Are rapidly absorbed from the intestine.</li> <li>● Are activated within the acidic medium of parietal cell canaliculi.</li> <li>● At neutral pH, PPIs are inactivated.</li> <li>● <b>Should not be combined with H<sub>2</sub>blockers or antacids.</b> Has to have a gap</li> <li>● Bioavailability is reduced by food.</li> <li>● Given one hour before the meal. Why should be given one hour before meal? To prevent gastroesophageal reflux (GER)</li> <li>● Have long duration of action (&gt; 12 h-24 h).</li> <li>● Once daily dose is sufficient.</li> <li>● Metabolized in the liver by Cyt-P450 , <b>dose reduction is required in severe liver failure.</b></li> </ul> <p>Should not be combined together because then we will have a BASIC medium when we need an acidic one.</p>			
Uses	<ul style="list-style-type: none"> <li>● Eradication of H. pylori (combined with antimicrobial drugs).triple therapy</li> <li>● Resistant severe peptic ulcer (4-8 weeks).</li> <li>● Gastroesophageal reflux disease (GERD).</li> <li>● <b>Hypersecretory conditions as Zollinger Ellison syndrome and gastrinoma (First choice).</b>excessive HCL</li> </ul>			

Gastric secretion by parietal cells →

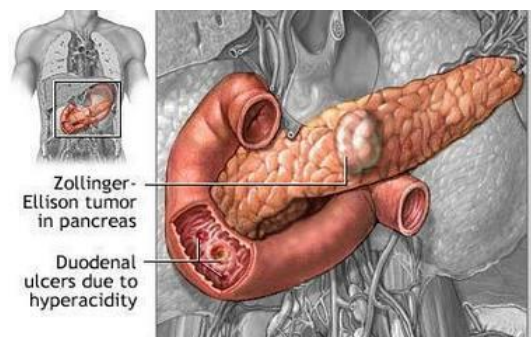


# Proton Pump Inhibitors (PPIs)

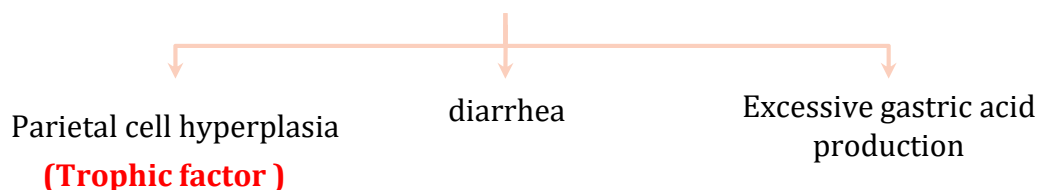
Drug	Omeprazole	Lansoprazole	Pantoprazole	Raprazole
ADRs	<ul style="list-style-type: none"> <li>● CNS: headache</li> <li>● GIT: diarrhea , abdominal pain } <span style="border: 1px dashed pink; padding: 2px;">Girl's Slides Only</span></li> <li>● <b>Achlorhydria</b> (no HCL) &amp; <b>Hypergastrinemia</b> (increased serum gastrin level).</li> <li>● <b>Gastric mucosal hyperplasia</b> ( results from high Gastrin → source of tumor)</li> <li>● <b>Infections</b> very imp!! ( Especially Respiratory tracts infections)               <ul style="list-style-type: none"> <li>-Increased bacterial flora <span style="font-size: small;">هاصت البكتيريا</span></li> <li>-Increased risk of community-acquired respiratory infections &amp; nosocomial pneumonia</li> </ul> </li> <li>● <b>Long term use may lead to:</b> interferes with absorption               <ul style="list-style-type: none"> <li>-Vitamin B12 deficiency , iron, calcium absorption</li> <li>-Hypomagnesemia which leads to decrease calcium</li> <li>-Osteoporosis (Increased risk of hip fractures)</li> </ul> </li> <li>● Precaution should be given not to combine Omeprazole (CYP2C19 inhibitor) and clopidogrel (CYP2C19) is required for activation of clopidogrel .</li> </ul>			

## Zollinger Ellison syndrome

Is a disease in which tumors cause the stomach to produce too much acid, resulting in peptic ulcers. symptoms include abdominal pain and diarrhea.



Gastrin produces



PPI is very effective

# H2 receptor blockers

Drug	Cimetidine	Ranitidine	Famotidine	Nizatidine
M.O.A	They <b>reversibly and competitively</b> block H <sub>2</sub> receptors on the parietal cells.			
P.K	<ul style="list-style-type: none"> <li>● Good oral absorption</li> <li>● Given before meals.</li> <li>● <b>Famotidine is the most potent drug.</b></li> <li>● Exposed to first pass metabolism</li> <li>● Duration of action (4-12 h).</li> <li>● Metabolized by liver.</li> <li>● Excreted mainly in urine.</li> </ul> <p><b>(except nizatidine that has the greatest bioavailability)</b></p>			
Actions	<ul style="list-style-type: none"> <li>● Reduce basal and food stimulated-acid secretion (less effective compared to PPIs).</li> <li>● Block 90% of <b>nocturnal acid secretion</b> (which depend largely on histamine) &amp; 60-70% of total 24 hr acid secretion. Therefore, it is better to be given <b>before night sleep</b> before sleeping histamine controls acid secretions more than other mediators.</li> <li>● What are the pharmacological actions of PPI and H2 blockers ? <b>Reduce pepsin activity.</b></li> <li>● Promote mucosal healing &amp; decrease pain</li> </ul>			
Uses	<ul style="list-style-type: none"> <li>● <b>GERD(heartburn/ dyspepsia).</b></li> <li>● <b>Acute ulcer healing in moderate cases</b> <ul style="list-style-type: none"> <li>- Duodenal Ulcer (6-8 weeks).</li> <li>- Benign gastric ulcer (8-12 weeks).</li> <li>- Prevention of <b>bleeding from stress-related gastritis.</b></li> </ul> </li> <li>● <u>Pre-anesthetic</u> medication (to prevent aspiration pneumonitis).</li> <li>● <u>Post-ulcer</u> healing maintenance therapy.</li> </ul>			
ADRs	<ul style="list-style-type: none"> <li>● Serious adverse effects are RARE</li> <li>● GIT disturbances: Nausea &amp; vomiting.</li> <li>● <b>CNS effects: Headache - confusion</b> (elderly, hepatic dysfunction, renal dysfunction).</li> <li>● <b>Bradycardia and hypotension (rapid I.V.)</b> inject slowly</li> <li>● <b>CYT-P450 inhibition (Only Cimetidine)</b> decrease metabolism of <b>warfarin, phenytoin</b>, benzodiazepines.</li> <li>● <b>Endocrine effects (Only Cimetidine)</b> Galactorrhea (Hyperprolactinemia) - <b>Antiandrogenic actions</b> (gynecomastia -impotence) due to inhibition of dihydrotestosterone binding to androgen Receptors.</li> </ul>			
Pre-cautions	Dose reduction of H2 Receptor blockers in severe renal or hepatic failure and elderly.			



	Cimetidine	Ranitidine	Famotidine	Nizatidine
<b>Efficacy</b>	+++	+++	+++	+++
<b>Potency</b>	+	++	+++ أقل جرعة	++
<b>Dose</b>	400 mg bid	150 mg bid	20 mg bid	150 mg bid
<b>Route</b>	Orally , IV	Orally , IV	Orally , IV	Orally
<b>T 1\2</b>	Short (2h)	Longer (3h)	Longer (3h)	Shortest (1h)
<b>Duration</b>	5-6 h	10 h	12 h	11 h
<b>CYT P450</b>	++	-	-	-
<b>Hormone antagonist Antiandrogenic</b>	++	-	-	-
<b>Drug inter-actions</b>	Many	No	No	No

#### Mnemonics:

Ranitidine= راني, Nizatidine= نيزار


راني و نيزار أصدقاء (Same efficacy , potency & dose )

(Ranitidine can be given orally & I.V) منذ القدم لكن بعد فترة قام راني بخيانة نيزار

(Nizatidine has the shortest T 1\2) نتيجة لهذه الفعلة اكتتب نيزار وتوعد

(Duration is more in Nizatidine) راني أن يرد له الصاع صاعين

(No drug interaction ) في النهاية اعترف راني بخطئه واعتذر لنيزار أصبحوا أصدقاء مرة أخرى

Special thank for Turki  
Alshammari 

## Prostaglandin analogues

Drug	Misoprostol
<b>M.O.A</b>	<ul style="list-style-type: none"> <li>● Prostaglandin analogues (PGE1)</li> <li>● Decrease HCL secretion</li> <li>● Increase protective measures ( increase mucous bicarbonate &amp; gastric mucosal blood flow )</li> </ul>
<b>P.K</b>	Orally , must be taken 3-4 times / day
<b>Indications</b>	Used for NSAIDs - induced peptic ulcer
<b>ADRs</b>	Abdominal cramps; diarrhea. Increase muscle contraction - Uterine contraction (dysmenorrhea or abortion). We use it in labor - Vaginal bleeding

# Antacids

<b>Drug</b>	<b>Inorganic salts: <math>\text{NaHCO}_3</math> - <math>\text{CaCO}_3</math> - <math>\text{Al(OH)}_3</math> - <math>\text{Mg(OH)}_2</math></b>
<b>M.O.A</b>	Acts by direct <b>chemical neutralization</b> of HCL and as a result may decrease pepsin activity.
<b>Indication</b>	<p>-Used to <b>relief pain (temporarily)</b> of peptic ulcer &amp; for dyspepsia.</p> <p>-All antacids ↓ absorption of some drugs as tetracycline, fluoroquinolones, iron. لان المذيبات تذيب أشباهها فالأدوية الأسيديك مارج تذوب</p> <p>No absorption for acidic drugs because we changed the PH</p> <p>-They usually use Aluminum hydroxide with Magnesium hydroxide to come over constipation and diarrhea.</p> <p><math>\text{NaHCO}_3</math> ( Sodium bicarbonate): no action on receptors just neutralizes Effective , but systemic alkalosis may occur</p>
<b>C.I</b> Only in $\text{NaHCO}_3$ (Sodium bicarbonate)	In CVS patients
<b>ADRs</b>	<p><b>Aluminum hydroxide :</b> <b>Constipation</b> -Systemic phosphate depletion (hypophosphatemia) (weakness , malaise , anorexia ) - Seizures.</p> <p><b>Magnesium hydroxide:</b> <b>Diarrhea used for constipation</b> تشدد الماء Cardiac arrest, hypotension</p> <p><b>Calcium carbonate :</b> - Milk-alkali syndrome -hypercalcemia -renal failure -decrease absorption of tetracycline. - (sodium bicarbonate is better absorbed then comes calcium carbonate)</p>

# Summary

## Proton Pump Inhibitors (PPIs): Most potent inhibitors of acid secretion

Drug	Omeprazole	Lansoprazole	Pantoprazole	Raprazole
MOA	● Irreversible inhibition of proton pump (H <sup>+</sup> / K <sup>+</sup> ATPase)			
P.D	● Heal ulcers faster than H <sub>2</sub> blockers, and have H. pylori inhibitory properties.			
P.K	<ul style="list-style-type: none"> <li>● Enteric coated formulations because unstable in acidic medium in stomach</li> <li>● Should not be combined with H<sub>2</sub> blockers or antacids.</li> </ul>			
Use	Zollinger Ellison syndrome and gastrinoma			
ADRs	Achlorhydria - Hypergastrinemia - Gastric mucosal hyperplasia Infection - Vit B12 deficiency - Hypomagnesaemia - osteoporosis			

## H<sub>2</sub> receptor blockers

Drug	Cimetidine	Ranitidine	Famotidine	Nizatidine
M.O.A	Reversibly and competitively.			
P.K	● Famotidine is the most potent drug.			
Action	● Block 90% of nocturnal acid secretion before night sleep.			
Uses	<ul style="list-style-type: none"> <li>● Acute ulcer healing in <u>moderate</u> cases</li> <li>● Prevention of bleeding from stress-related gastritis.</li> </ul>			
ADRs	<ul style="list-style-type: none"> <li>● Headache - confusion - Bradycardia and hypotension (rapid I.V.)</li> <li>● Cimetidine only: 1-CYT-P450 inhibition (drug interaction)</li> <li>2-Endocrine effects: Galactorrhea (Hyperprolactinemia) - Antiandrogenic actions (gynecomastia -impotence)</li> </ul>			

## Prostaglandins analogue

Drug	Misoprostol
M.O.A	<ul style="list-style-type: none"> <li>● Decrease HCL secretion</li> <li>● Increase protective measures (↑mucous bicarbonate &amp; gastric mucosal blood flow)</li> </ul>
Use:	NSAIDs - induced peptic ulcer

## Antacids

Drug	Calcium carbonate CaCO <sub>3</sub>	Sodium bicarbonate NaHCO <sub>3</sub>	Aluminum hydroxide Al(OH) <sub>3</sub>	Magnesium hydroxide Mg(OH) <sub>2</sub>
M.O.A	Acts by direct chemical neutralization of HCL			
ADAs	Milk-alkali syndrome Renal failure	-	Constipation	Diarrhea

# Summary From Prof.Hanan's Slide

- 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<sub>2</sub> receptor blockers
  - PPIs should be used for acute therapy only if H2RAs 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

# MCQs

1- a patient came complaining from abdominal pain and diarrhea. Blood tests showed elevated gastrin levels. Biopsy revealed a tumor that was the cause of the excess gastrin production. Which drug is your first choice?

- A- Cimetidine.
- B - Misoprostol.
- C- Omeprazole.
- D- pyrazinamide.

2- which of the following is true about proton pump inhibitors?

- A- unstable in acidic medium.
- B- activated in the duodenum.
- C- can be safely combined with H2 blockers.
- D- activated at neutral pH.

3- which of the following forms of prostaglandin has a protective function of the gastric mucosa?

- A- PGD2
- B- PGI2
- C- PGF2a
- D- PGE1

4- all of the following are classified as hyposecretory drugs except :

- A- proton pump inhibitors.
- B- prostaglandin analogues.
- C- H2 receptor blockers.
- D- antimuscarinic drugs .

5- a patient suffering from peptic ulcer suddenly developed pneumonia. Which of the following drugs was he most likely on ?

- A- Ranitidine.
- B- atropine.
- C- pyrazinamide.
- D- Pantoprazole.

6- ahmad suffers from cardiovascular disorders and he is put on lifelong clopidogrel to prevent strokes and myocardial infarctions. Recently he has been diagnosed with a peptic ulcer. Which of the following drugs is absolutely contraindicated in his case ?

- A- pantoprazole
- B- lansoprazole
- C- omeprazole
- D- raprazole.

- 1-C
- 2-A
- 3-B
- 4-B
- 5-D
- 6-C

## MCQs:

7- a patient comes complaining of epigastric pain and heartburn that wakes him up during his sleep at night. Drug history of the patient reveals that he is on warfarin. Which is the best drug to be prescribed in this case?

- A- omeprazole.
- B- misoprostol.
- C- famotidine
- D- Cimetidine.

8- which adverse effect of H<sub>2</sub> receptor blockers will be **most evident** in elderly patients , or with patients with hepatic\renal dysfunction ?

- A- nausea and vomiting.
- B- bradycardia.
- C- galactorrhea.
- D- headache and confusion.

9- a patient came complaining from impotence and gynecomastia. After taking history , he revealed that he had a recent peptic ulcer which he took medication for. Which of the following drugs was he on?

- A- ranitidine.
- B- cimetidine.
- C- famotidine.
- D- omeprazole.

10- a patient was taking medications for his knee pain for a long time, later he developed epigastric pain, nausea and vomiting. Which one of the following drugs is best used for is treatment?

- A- misoprostol.
- B- cimetidine.
- C- famotidine.
- D- omeprazole.

7-C  
8-D  
9-B  
10-A

## SAQ:

**Q1: list three of the antacids and a characteristic side effect of each one.**

**Drug :** CaCO<sub>3</sub> or calcium bicarbonate

**Side effect :** Milk- alkali syndrome , hypercalcemia , and renal failure.

**Drug:** Mg(OH)<sub>2</sub> or magnesium hydroxide

**Side effect:** diarrhea

**Drug:** Al(OH)<sub>3</sub> or Aluminium hydroxide

**Side effect:** constipation , hypophosphatemia , seizures.

**Q2: a patient is complaining of epigastric pain and heartburn , nausea & vomiting , and dark \ tarry stool. He was diagnosed with a peptic ulcer. Tests showed the presence of H pylori.**

**Which class of hyposecretory drugs can be incorporated in the triple therapy of H pylori?**

Proton pump inhibitors.

**What is their mechanism of action ?** they act by irreversible inhibition of proton pump H<sup>+</sup>/k<sup>+</sup> ATPase that is responsible for final step in gastric acid secretion from parietal cells.

**List two common side effects :**

- 1- Achlorhydria & hypergastrinemia
- 2- Vitamin B12 deficiency upon long term use.

## Team leaders:

Ghaida Saad Alsanad

Majed Aljohani

## Sub leader:

Laila Alsabbagh

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## References:

✓ Doctors' slides and notes



@Pharma4370



Pharm437@gmail.com