



# 1: Peptic ulcer

## 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 cyoprotective 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.

## Color index

● extra information and further explanation

● important

● doctors notes

● Drugs names

● Mnemonics



 [Kindly check the editing file before studying this document](#)

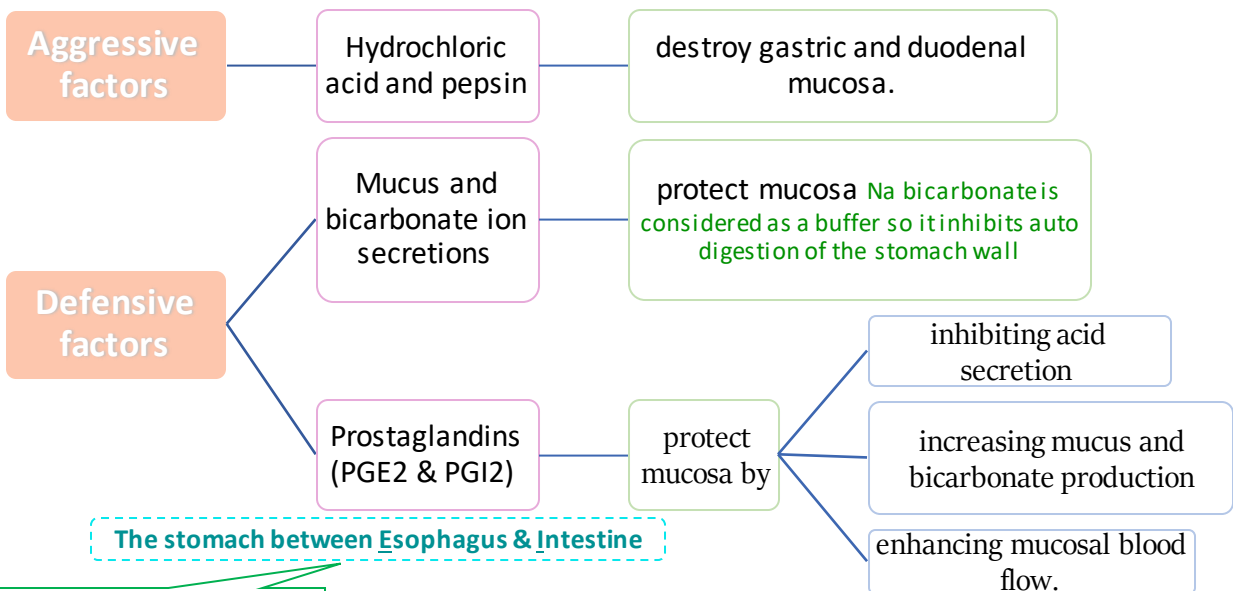
# Introduction

## Peptic ulcer disease (PUD)

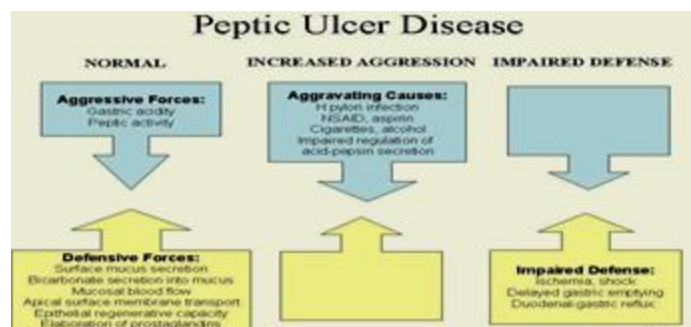
- a localized lesion of the mucous membrane of the stomach (gastric ulcer) or duodenum (duodenal ulcer), typically extending through the muscularis mucosa.

## Pathophysiology

- is imbalance between aggressive factors (acid & pepsin) and defensive factors (e.g. prostaglandins, mucus & bicarbonate layer).
- However, nowadays, it seems that *H. pylori* is a major cause



One of the main action of Prostaglandins is increase the turnover and regeneration of damaged cells



## Etiology

- H. pylori* infection** is the major etiological factor in peptic ulcer disease (95% in duodenal and 80% in gastric ulcer).
- Drugs (e.g.) NSAIDs; corticosteroids,
- Hypersecretory states (Zollinger Ellison syndrome) “**gastrin inducing tumor**”
- Alcohol
- Smoking
- Caffeine
- Diet “Spicy food”
- Genetic factors “O blood group are susceptible to have peptic ulcer”

When a Pt. comes with peptic ulcer first thing we must do is excluding of *H. pylori* because its treatment is totally different

# Introduction

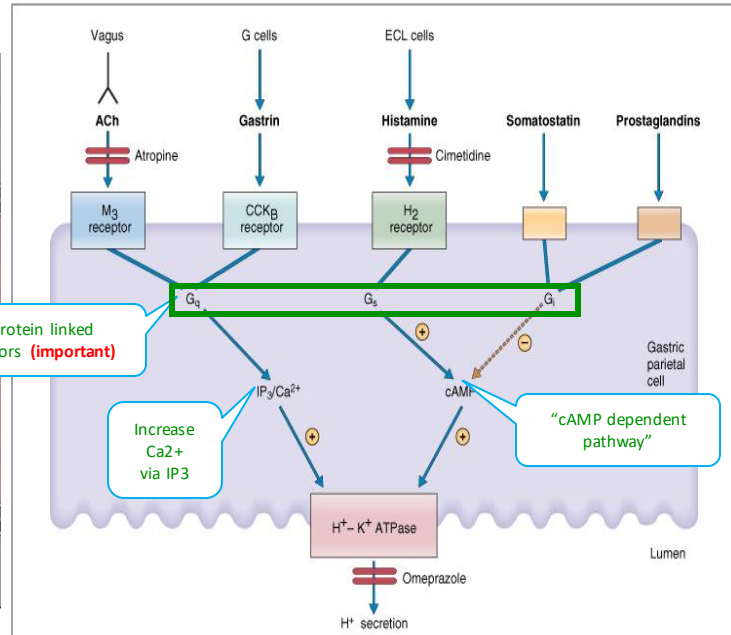
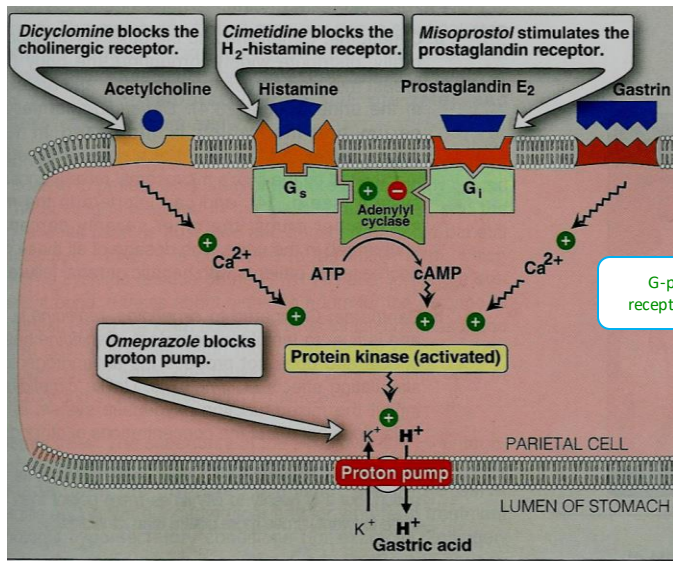
## Gastric secretions

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

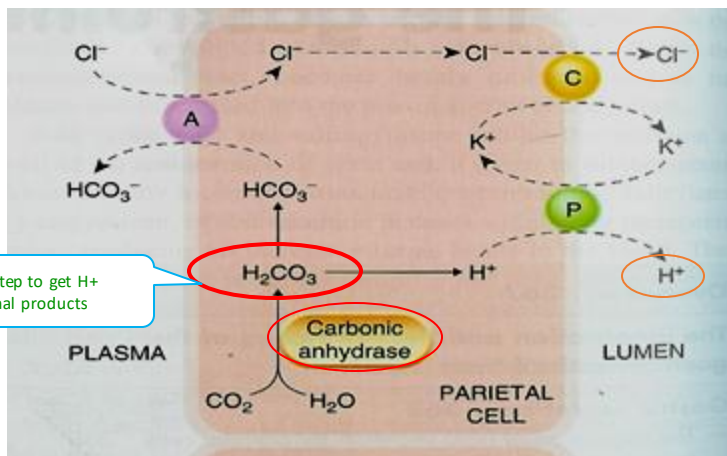
## Regulation of gastric secretions

Parietal cells secrete acid in response to:

- 1- Ach (neurotransmitter): M<sub>3</sub> receptors. **It is not effective alone**
- 2- Gastrin (hormone): CCK<sub>2</sub> receptors (cholecystinin) **it's NOT approved yet**
- 3- Histamine (local hormone): H<sub>2</sub> receptors
- 4- Proton pump (H<sup>+</sup>/ K<sup>+</sup> ATPase)



## Gastric secretion by parietal cells



Its formation is an important step to get H<sup>+</sup> and HCO<sub>3</sub><sup>-</sup> to make HCl as a final products

# Overview on the treatment of peptic ulcer

Two types of treatment (antibiotics) for H.pylori are:  
 1-triple treatment 2- Quadra treatment but when we use other agents symptoms will be relieved for a while . After finishing of treatment assessment must be done to make sure of complete eradication .

Eradication of H. pylori infections

Hyposecretory drugs

Decrease gastric acid secretion to promote healing and pain relief

Mucosal cytoprotective agents

Neutralizing agents (antacids)  
 Not treatment

Proton pump inhibitors  
 برا فيه زول قوي

H2 receptor blockers

Antimuscarinic drugs

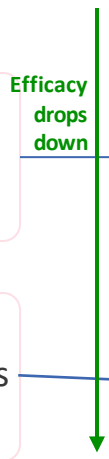
Prostaglandin analogues

NaHCO3 Sodium bicarbonate

Aluminum hydroxide Al(OH)3

Mg(OH)2 Magnesium hydroxide

CaCO3 Calcium carbonate



Lansoprazole  
Pantoprazole  
Omeprazole  
Raprazole

(لانسوا) شكلهم اني (ينت) (امي) ويحسبون مالي (ري) زين، (برا يا زول)

Nizatidine  
Ranitidine  
Cimetidine  
Famotidine

(نزار) انقذ حياة (ران) وسحب (سم) العقرب (بفمو)، عشان كذا هي (تدين له) بحياتها مرتين

Misoprostol

# Proton Pump Inhibitors (PPIs)

Drug	<b><u>Omeprazole</u> , <u>Lansoprazole</u> , <u>Pantoprazole</u> , <u>Raprazole</u></b>
Mech. of action	Acts by <b>irreversible (long effect) 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).
Pharmacodynamics	<ul style="list-style-type: none"> <li>They are the most potent inhibitors of acid secretion available today.</li> <li>Produce marked inhibition of basal <b>H2 receptors</b> &amp; <b>meal stimulated-acid secretion</b> (90-98%).</li> <li>Reduce pepsin activity.</li> <li>Promote mucosal healing &amp; decrease pain.</li> <li><b>Proton pump inhibitors heal ulcers faster than H2 blockers, and have H. pylori inhibitory properties.</b> One of triple therapy is PPIs (so they have Bactericidal &amp; inhibitory effects because this organism need acidic medium to survive)</li> </ul>
Pharmacokinetics	<ul style="list-style-type: none"> <li>Given orally</li> <li>Are pro-drugs (given inactive, converts to the active form after metabolism in the body)</li> <li>Given as <b>enteric coated formulations (unstable in acidic medium in stomach)</b>. <span style="border: 1px solid black; border-radius: 15px; padding: 2px;">To prevent the stomach from breaking it down and reach the intestine</span></li> <li>Are rapidly absorbed from the intestine.</li> <li><b>Are activated within the acidic medium of parietal cell canaliculi.</b></li> <li>At neutral pH = 7, PPIs are inactivated. <i>Such as in blood</i></li> <li>Should <b>NOT</b> combined with H2 blockers or antacids. <span style="border: 1px solid black; border-radius: 15px; padding: 2px;">We shouldn't administer it with anything that lowers the stomach acid secretions even more! These drugs already have a long effect.</span></li> <li>Bioavailability is reduced by food.</li> <li>Given one hour before the meal. <b>On empty stomach</b></li> </ul> <p><i>Why should be given one hour before meal? While they reach intestine the Pt. started eating → food stimulates parietal cells to produce HCl and meanwhile PPIs started to give their effect</i></p> <ul style="list-style-type: none"> <li>Have long duration of action (&gt; 12 h-24 h). -&gt; Once daily dose is sufficient</li> <li>Metabolized in the liver by Cyt-P450. <i>although they get metabolized within one hour but their duration of action is long since they block the H<sup>+</sup>/K<sup>+</sup> ATPase irreversibly</i></li> <li>Dose reduction is required in severe liver failure.</li> </ul>
Indications	<ul style="list-style-type: none"> <li>Eradication of H. pylori (combined with antimicrobial drugs).</li> <li>Resistant severe peptic ulcer (4-8 weeks). <i>They are expensive so it's reserved for severe cases</i></li> <li>Gastroesophageal reflux disease (GERD or GORD).</li> <li><b>Hypersecretory conditions as Zollinger Ellison syndrome</b> will be explained later and <b>gastrinoma (First choice)</b>. M3 &amp; H2 blockers can treat Zollinger Ellison syndrome but we choose PPIs why? because <i>they treat at lower dose (double or triple normal dose) comparing to H2 &amp; M3</i> <span style="border: 1px dashed black; border-radius: 10px; padding: 2px;">المشكلة في هذا المرض هي زيادة الاحماض فأى دواء ينوصف راح يكون بجرعة أكبر من المعتاد</span> <span style="border: 1px dashed black; border-radius: 10px; padding: 2px;">Prazole = zollinger</span></li> </ul>
ADRs	<ul style="list-style-type: none"> <li><b>CNS:</b> Headache</li> <li><b>GIT:</b> Diarrhea &amp; abdominal pain.</li> <li>Achlorhydria (absence of HCL) leads to Hypergastrinaemia but how? <i>The stomach sense the high PH low acidity effect of the drug so it sends signals to gastrin producing cells to secrete more gastrin but the pump IS STILL inhibited so it sends more signals to produce gastrin</i></li> <li><b>reflex Hypergastrinaemia.</b> <i>Is a trophic factors cause hyperplasia of parietal cells on lab animals not humans safe</i></li> <li>Gastric mucosal hyperplasia can cause: <ul style="list-style-type: none"> <li>-Increased bacterial flora <i>because HCl is reduced</i></li> <li>-Increased risk of community-acquired respiratory infections &amp; nosocomial pneumonia</li> </ul> </li> </ul> <p><b>∴ if used in a Long term use may lead to :</b></p> <ul style="list-style-type: none"> <li>Vitamin B12 deficiency, iron, calcium absorption. <i>reducing the acidity of stomach can prevent it from digesting proteins</i></li> <li>Increased risk of hip fractures due to deficiency <i>not advisable for long term use</i></li> </ul> <p><b>Precaution should be given NOT to combine omeprazole (CYP2C19 inhibitor) and clopidogrel antiplatelet like aspirin (CYP2C19 is required for activation of clopidogrel).</b> <i>It increase the risk of cardiovascular thrombus</i></p> <div style="border: 1px dashed black; border-radius: 10px; padding: 5px; display: inline-block;">         (Ome-prazole) إلا أمي (clo-pido-grel) كلو بدو بنات     </div>

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

Drug	<b>Cimetidine</b> not available in KSA , <b>Ranitidine</b> , <b>Famotidine</b> , <b>Nizatidine</b>
Mech. action	They <b>reversibly and competitively</b> (will be dissociated from receptors if agonist conc. Is higher) block H <sub>2</sub> receptors on the parietal cells. <b>They are cheap drugs</b>
Pharmacodynamics	<ul style="list-style-type: none"> <li>• <b>Block 90% of nocturnal acid secretion</b> (which depend largely on histamine) &amp; <b>60-70%</b> of total 24 hr acid secretion. Therefore, it is better to be <b>given before night sleep</b>. <b>before sleeping histamine controls acid secretions more than other mediators</b></li> <li>• Reduce pepsin activity.</li> <li>• Promote mucosal healing &amp; decrease pain</li> <li>• Reduce basal and food stimulated-acid secretion</li> </ul>
Pharmacokinetics	<ul style="list-style-type: none"> <li>* Good oral absorption</li> <li>* Given before meals.</li> <li>* <b>Famotidine</b> is the most <b>potent</b> drug. <b>The family is the most potent supporter in our lives</b></li> <li>* <b>Exposed to first pass metabolism</b> (metabolized before reaching the blood circulation) (<b>except nizatidine that has the greatest Bioavailability = conc. of active drug in blood circulation after administration</b>) <b>نزار قباني وصل صوت المرأة لكل مكان بشعره</b></li> <li>* Duration of action (4-12 h).</li> <li>* Metabolized by liver.</li> <li>* Excreted mainly in urine.</li> </ul>
Indications	<ul style="list-style-type: none"> <li>- GERD (heartburn/ dyspepsia).</li> <li>- Acute ulcer healing in <b>moderate</b> cases <ul style="list-style-type: none"> <li>* Duodenal Ulcer (6-8 weeks).</li> <li>* Benign gastric ulcer (8-12 weeks).</li> <li>* Prevention of bleeding from stress-related gastritis.</li> </ul> </li> <li>- <b>Pre-anesthetic</b> medication (to prevent aspiration pneumonitis). <b>2 Hours before surgery =H<sub>2</sub> blockers</b></li> <li>- Post-ulcer healing maintenance therapy. <b>After complete eradication of H.pylori</b></li> </ul> <p>لما يكون المريض منوم ممكن يصير ارتجاع لحمض المعدة فيدخل على الرئة ويسوي التهاب</p>
ADRs	<ul style="list-style-type: none"> <li>▪ <b>GIT disturbances:</b> Nausea &amp; vomiting.</li> <li>▪ <b>CNS effects:</b> Headache - confusion</li> </ul> <p><b>(Contraindicated in elderly, hepatic dysfunction, renal dysfunction).</b></p> <ul style="list-style-type: none"> <li>▪ Bradycardia and hypotension (if given in rapid I.V.) <b>so must be given slowly</b></li> <li>▪ <b>CYT-P450 inhibition (Only Cimetidine) decrease</b> metabolism of warfarin <b>increase risk of bleeding</b> , phenytoin, benzodiazepines. Which causes the T1/2 to prolong</li> <li>▪ <b>Endocrine effects (Only Cimetidine)</b> <ul style="list-style-type: none"> <li>▪ Galactorrhea (Hyperprolactinemia ) <b>risk if infertility</b></li> <li>▪ <b>Antiandrogenic actions (gynecomastia –impotence)</b> due to inhibition of dihydrotestosterone binding to androgen receptors.</li> </ul> </li> </ul> <p>مثل السع شين</p>
Notes	<p><b>Precautions</b></p> <p>Dose reduction of H<sub>2</sub> receptor blockers in severe renal or hepatic failure and elderly.</p>

# For better understanding

## H2 receptor blockers

	CIMETIDINE	RANITIDINE	FAMOTIDINE	NIZATIDINE
<b>Efficacy</b> is equal	+++	+++	Most potent +++	+++
<b>Potency</b>	+	++	+++	++
<b>Dose</b>	400 mg bid	150 mg bid	20mg bid	150 mg bid
<b>Route</b>	orally, IV	orally, IV	orally, IV	orally
<b>T 1/2</b>	short (2 h)	longer (3h)	longer (3h)	shortest (1 h)
<b>Duration</b>	5-6 h	10 h	12 h	11 h
<b>CYT P 450</b>	++	-	-	-
<b>Antiandrogenic</b>	++	-	-	-
<b>Drug interactions</b>	many	No	No	No

Lowest dose, most potent

Due to its side effects it is not available in KSA

مثل السم شين

## 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-secreting tumor of the pancreas.

### Gastrin results in:

- Parietal cell hyperplasia (trophic factor).
- Excessive gastric acid production.



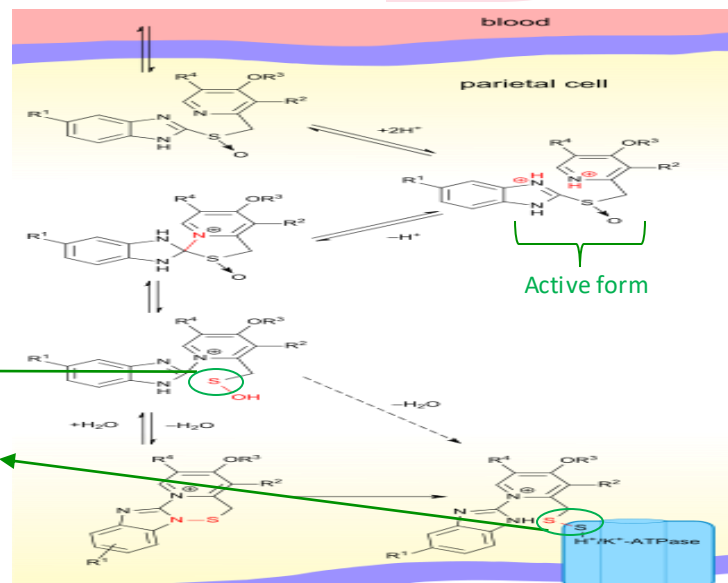
Zollinger-Ellison syndrome is a rare condition in which one or more tumors form in your pancreas or the upper part of your small intestine (duodenum). These tumors, called gastrinomas, secrete large amounts of the hormone gastrin, which causes your stomach to produce too much acid. The excess acid then leads to peptic ulcers, as well as to diarrhea and other symptoms

## Activation of Proton Pump Inhibitors In Parietal cell

first it reaches the intestine as prodrug get inside the parietal cells → activated by protonation (adding hydrogen ions) and this must happen in acidic medium within parietal cells

Sulfur atom

Makes a covalent bond with H<sup>+</sup>/K<sup>+</sup> ATPase sulfur atom which is a strong bond



# Prostaglandin analogues

Drug	<p style="text-align: center;"><b>Misoprostol</b></p> <p>Prostaglandin analogues (PGE1 ) why we use analogues instead of the actual prostaglandin ? prostaglandins have very short duration of action (minutes)</p>		
P.D	<p>↓ HCL secretion.                  ↑ protective measures (↑ mucous/bicarbonate &amp; gastric mucosal blood flow).</p>		
P.K	Orally, must be taken 3-4 times/day. (short duration of action)		
uses	Used for NSAIDS-induced peptic ulcer.		
ADRs	Abdominal cramps; diarrhea.	الأنة (miss) أجهضت (miscarriage) طفلها Uterine contraction (dysmenorrhea or abortion) Be careful with pregnant women Vaginal bleeding.	

# Antacids

These drugs are mainly inorganic salts (basic substance NOT treatment)

Drug	Sodium bicarbonate $\text{NaHCO}_3$ Na is well absorbed	Aluminum hydroxide $\text{Al(OH)}_3$ It isn't well absorbed	Magnesium hydroxide $\text{Mg(OH)}_2$ It isn't well absorbed	Calcium carbonate $\text{CaCO}_3$ It isn't well absorbed
M.O.A	acts by direct chemical neutralization of HCL and as a result may decrease pepsin activity.			
uses	used to relief pain of peptic ulcer & for dyspepsia.			
ADRs	Effective, but systemic alkalosis may occur.	<ul style="list-style-type: none"> <li>Constipation ألم المغص شين</li> <li>Systemic phosphate depletion (weakness, malaise, anorexia) in high doses</li> </ul> It's not well absorbed , but due to prolong use it might get absorbed and cause these side effects	<ul style="list-style-type: none"> <li>Diarrhea مات وكان ماجن وقليل حياء</li> <li>Magnesium trisilicate-- slow-acting antacid</li> </ul>	<ul style="list-style-type: none"> <li>Milk-alkali syndrome happens when there is high source of Ca or production with alkalosis</li> <li>Hypercalcemia</li> <li>Renal failure</li> </ul>
Contra-indications	CVS patients since Na may cause water retention	They usually use Aluminum hydroxide with Magnesium hydroxide to come over constipation and diarrhea		
Notes	<ul style="list-style-type: none"> <li>All antacids ↓ absorption of some drugs as : Tetracycline Deposition in the bone &amp; teeth , fluoroquinolones, iron. (There must be gap at least 2 hours between their admiration with antacids)</li> </ul>			



# Summary

- Peptic ulcer disease happens due to the imbalance between **aggressive factors** ( HCL/pepsin ) and the **defensive factors** ( mucus/ HCO<sub>3</sub>/prostaglandins )
- Major etiological cause is **H. Pylori infection**

## Treatment of PUD

Eradication of H. pylori infection

Hyposecretory drugs

Mucosal cytoprotective agents

Neutralizing agents

**1- PPI :** Omeprazole , Lansoprazole , pantoprazole , Raprazole

- Acts by **Irreversible inhibition of Proton pump** by covalent " di-sulphate " bond
- Most potent hyposecretory drugs.
- **Have H.pylori inhibition effect.**
- **Marked inhibition in basal and meal stimulates-acid secretion.**
- Never combined with H<sub>2</sub> blockers or Antacids
- Used for resistant and **sever** cases.
- **1<sup>st</sup> choice for treating Zollinger Ellison**
- May cause Hyperplasia in parietal due to reflex hypergastrinaemia due to Achlorhyria ( absence of HCl).
- Long term use may lead to Vitamin & iron deficiency, calcium absorption and increase the risk of hip fracture.

**Prostaglandin analogues**  
Misoprostol

- Increase protective measures (Increase mucous/bicarbonate & gastric mucosal blood flow/ decrease HCl).
- **Used for NASID-induced peptic ulcer.**
- May cause **uterine contraction (abortion)** and vaginal bleeding and Abdominal cramps; diarrhea.

**Inorganic basic salts**  
**Not treatment**

- Neutralizes HCL .
- used to relief pain of peptic ulcer & for dyspepsia.
- Decrease absorption of: Tetracycline ,fluoroquinolones , Iron

**1- NAHCO<sub>3</sub> :**  
may cause systemic alkalosis  
○ C.I in CVS patients

**2- Aluminum hydroxide:**  
cause constipation and systemic phosphate depletion.

**3- Magnesium Hydroxide:**  
cause diarrhea

**# 2&3 are given together to antagonize each other's ADR**

**4- calcium carbonate:**  
cause milk-alkali syndrome , renal failure

• **OMEPRAZOLE which is a very potent liver enzyme inhibitor, should not be combined with CLOPIDOGREL which is anti-platelet that is Activated by CYP2C19.**

**2- H2 blockers :** Cimetidine , Famotidine , Ranitidine , Nizatidine

- Reversible & competitive block of H<sub>2</sub> receptor.
- Used for moderate cases.
- **Block Nocturnal acid secretions better given before sleep**
- Pre-anesthetic to prevent aspiration pneumonitis.
- Used as Post-ulcer healing maintenance therapy.
- **Famotidine** is the most potent drug.
- **nizatidine** that has the greatest bioavailability.
- **Cimetidine** have **Antiandrogenic** effects and may cause **gynecomastia**.
- **Cimetidine CYT-P450 inhibition** decrease metabolism of other drugs.

# MCQs

**1- 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 of the following choices should be avoided in this patient?**

- A. Famotidine                      B. Omeprazole                      C. Misoprostol

**2- Which of the following medications for gastrointestinal problems is contraindicated in pregnancy and may lead to abortion ?**

- A. Famotidine                      B. Omeprazole                      C. Misoprostol

**3- If we have a patient with cardiovascular disease who is taking aspirin as one of his medications, which one of the following anti-ulcer drugs will be recommended in his case?**

- A. Famotidine                      B. Omeprazole                      C. Misoprostol

**4- 28 years old female has heartburn pain almost 5 days in a week, especially after the meals. Which one of the following drugs will be the best choice in her case ?**

- A. Cimetidine                      B. Lansoprazole                      C. Misoprostol

**5- 41 years old male has heartburn pain, especially at the night during sleeping . Which one of the following drugs will be the best choice in his case ?**

- A. Famotidine                      B. Lansoprazole                      C. Misoprostol

**6- Which one of the following is serious complication of prolong use of H2 blockers & Proton Pump inhibitors ?**

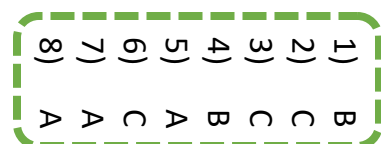
- A. Adenocarcinoma                      B. gynecomastia                      C. Pseudomembranous colitis

**7- 22 years old female with Extra hair on her face and body and irregular periods. She is diagnosed with polycystic ovary syndrome and high level of androgens hormone. If she has peptic ulcer which one of the following anti-ulcer drug will be recommended in her case?**

- A. Cimetidine                      B. Lansoprazole                      C. Misoprostol

**8- Which one of the following drugs may cause gynecomastia and impotence in male ?**

- A. Cimetidine                      B. Famotidine                      C. Nizatidine



# MCQs

**9- Which one of the following drugs may lead to excessive bleeding if it combines with warfarin ?**

- A. Cimetidine                      B. Famotidine                      C. Nizatidine

**10- Which one of the following drugs does not exposed to first pass metabolism in the liver and has high bioavailability to be taken orally ?**

- A. Cimetidine                      B. Famotidine                      C. Nizatidine

**11- Patient is diagnosed with gastrin-secreting tumor of the pancreas and he develop peptic ulcer due to excessive gastric acid production. Which one of the following is drug of choice ?**

- A. Famotidine                      B. Omeprazole                      C. Misoprostol

**12- Which one of the following drugs can be used before surgery to prevent aspiration pneumonitis ?**

- A. Famotidine                      B. Omeprazole                      C. Misoprostol

**13- Which one of the following antacids may cause constipation?**

- A. Sodium bicarbonate              B. Aluminum hydroxide              C. Magnesium hydroxide

**14- Which one of the following antacids may cause Diarrhea ?**

- A. Sodium bicarbonate              B. Aluminum hydroxide              C. Magnesium hydroxide

**15- Which one of the following antacids may cause water retention and increase the preload in patients with cardiovascular disease ?**

- A. Sodium bicarbonate              B. Aluminum hydroxide              C. Magnesium hydroxide

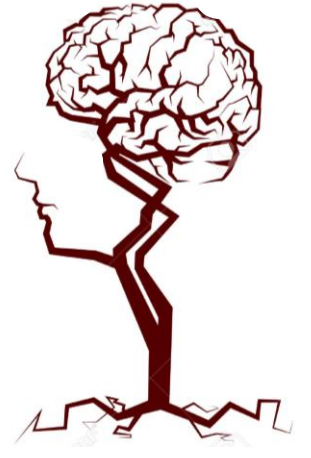
**16- Which one of the following anti-ulcer drug may combine with antibiotic to treat H.pylori infections ?**

- A. Famotidine                      B. Omeprazole                      C. Misoprostol

**17- Which one of the following hyposecretory drugs is the potent one, and act as Proton pump inhibitors ?**

- A. Famotidine                      B. Omeprazole                      C. Misoprostol

9)	A
10)	C
11)	B
12)	A
13)	B
14)	C
15)	A
16)	B
17)	B



إِنَّ فِي ذَلِكَ لَآيَاتٍ لِّقَوْمٍ يَتَفَكَّرُونَ ﴿٣﴾

## قادة فريق علم الأدوية :

- جومانا القحطاني - اللولو الصليهم
- فارس النفيسة

## الشكر موصول لأعضاء الفريق المتميزين :

عبد الرحمن ذكري

روان القحطاني

شذا الغيهم

شوق الأحمري

وثام بابعير

### References :

- 1- 436 doctor Hanan's slides and notes
- 2- [www.mayoclonic.org](http://www.mayoclonic.org)
- 3- 436 doctor Ishfaq Notes



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