Unit V – Problem 4 – Pharmacology: Proton-Pump Inhibitors (PPIs)

- **Acid-Antisecretory agents:**
  - **Proton pump inhibitors:**
    - ✓ They end with (-prazole).
    - ✓ The main drug is omeprazole (you have to memorize this drug).
    - ✓ Other drugs include: dexlansoprazole – esomeprazole – lansoprazole – pantoprazole – rabeprazole
  - **Mechanism of action**: irreversible inhibition of the H^+/K^+ ATPase of the parietal cells of the stomach (by forming S-S sulfonamide) thus inhibiting the secretion of H^+.
  - PPIs are given as enteric-coated granules in capsules or enteric-coated tablets, because:
    - ✓ This prevents premature activation by the gastric low pH.
    - ✓ Reducing the first-pass effect & thus increasing the bioavailability of the drug.
    - ✓ Increasing the absorption in small intestine where the pH is alkaline.
  - **Adverse effects** include those in GIT, headache, drug-drug interactions & hypergastrinemia.
- **H_2 – receptor antagonists:**
  - They end with (-tidine).
  - The main drug is cimetidine (you have to memorize this drug).
  - **Other drugs include**: famotidine – nizatidine – ranitidine.
  - **Mechanism of actions**: competitive reversible inhibition of the binding of histamine to H_2-receptors which are present on the parietal cells of the stomach. Normally, histamine causes acid secretion but this will be inhibited by using these drugs.
  - **Adverse effects**: CNS (esp. when given IV & in high doses to elderly); drug-drug interactions; decreasing testosterone binding to androgen receptors, inhibiting estradiol metabolism, elevating serum prolactin levels; Vitamin B12 deficiency.

Differences between H_2 Blockers and PPIs

	H_2 Blockers	PPIs
Mode of action	Block H_2-receptor of parietal cells by a competitive reversible mechanism.	Converted to active form irreversibly inactivates H^+/K^+-ATPase.
Inhibition of total 24-hour acid secretion	60 – 70%[a]	90 – 98%[b]
Half-life time (t½)	1 – 4 hours, given bid or qid.	0.5 – 2 hours[c] Almost given qid/bid.
Pharmacological tolerance	Develop	Does not develop[d]
Rebound acid hyper-secretion	May occur following discontinuation	May occur following discontinuation
Dosage adjustment	• Severe liver impairment • Renal impairment(↓GF)	Liver disease

[a] = Markedly suppress nocturnal acid secretion but have a modest effect on meal-stimulated (postprandial) acid secretion.

[b] = Block the final pathway (step) of gastric acid secretion + markedly suppress nocturnal and meal-stimulated (postprandial) acid secretion.

[c] = Inhibition of acid secretion lasts up for 24 hours due to irreversible inactivation of PP.

[d] = Because increased gastric-mediated histamine release cannot overcome blockade of PP.

- **Mucosal protective agents:**
  - **These include**: bismuth – sucralfate – prostaglandin analogues (misoprostol) & antacids (مضادات حموضة المعدة). Antacids are either systemic ($NaHCO_3$: causing metabolic alkalosis) or non-systemic such as:
  - $Al(OH)_3$: causing constipation.
  - $Mg(OH)_2$: causing diarrhea.
- **H.Pylori eradication therapy:**
  - **The most effective regimen**: is the combination of two antibiotics and a proton pump inhibitor.
  - *Triple therapy*: clarithromycin + amoxicillin or metronidazole + PPI
  - *Quadruple therapy*: bismuth + metronidazole + tetracycline + PPI or H_2-receptor blocker.
  - *Sequential therapy*: clarithromycin + amoxicillin + metronidazole + PPI