PPIs & H2 antagonists

Lecture 2

Prof. Ahmed Shaaban

Professor of Pharmacology &

Senior consultant of Endocrinology

Proton Pump Inhibitors (PPIs)

1. Omeprazole & esomeprazole.
2. Lansoprazole.
3. Pantoprazole.
4. Rabeprazole.

Mechanism

A) Acid - suppression:

The most potent and highest efficacy acid – suppressant.

Absorbed in intestine reaching parietal cells from circulation and diffuse into secretory canaliculi where they are pronated and trapped.

They interact with SH groups of H+ / K+ ATPase → enzyme inhibition → ↓H+ pump → ↓ Hcl secretion. This maintains intragastric pH more than 4 for at least 20 hours, causing effective nocturnal and day - time acid suppression.

B) Anti H pylori:

Lansoprazole is the most potent PPI against H pylori.

Pharmacokinetics

PPIs are acid – labile prodrugs. For protection from rapid destruction within gastric lumen, oral formulations for delayed release as acid resistant, enteric coated capsules or tablets are used. In alkaline intestinal lumen, enteric coatings dissolve causing absorption of prodrugs.

Absorption orally is rapid, pantoprazole more than lansoprazole than omeprazole.

IV injection allows more of drugs to reach site of action in parietal cell canaliculi without degradation.

Onset of action: 1 hour.

Peak: 2 hours.

Bioavailability

Pantoprazole (90%), lansoprazole (80%) & omeprazole (60%).

Decrease markedly (50%) by food in case of lansoprazole & omeprazole (must be given at least 30 minutes before meals). Pantoprazole is unaffected by food (given before, during or after meals).

Bioavailability of omeprazole is increased after repeated dosing. Esomeprazole is S- isomer of omeprazole. It has 80% bioavailability.

Rapid 1st pass and systemic hepatic metabolism (affected by liver function).

Serum t ½ is 1 hour but duration of action is more than 24 hours due to prolonged inhibition of H+ / K+ ATPase.

Uses

1st line in PU disease.

1.DU: for 2-8 weeks.

Specially in severe and non responding mild or moderate cases.

It produces faster pain relief and more rapid ulcer healing than H2 antagonists. Healing rates are higher. Pantoprazole is more potent and has higher efficacy and produces faster symptom relief than lansoprazole than omeprazole.

2. GU: for 4-8 weeks.

3. Prevention of rebleeding from PU and stress bleeding. High oral dose or IV infusion increases intragastric pH > 6 and increases coagulation and platelet aggregation.

4. GERD: Longer term use is frequently required.

- Mild cases: lansoprazole is the drug of 1st choice because its rapid absorption leads to more efficient acid suppression.
- Severe cases: omeprazole is the drug of 1st choice because, unlike lansoprazole and pantoprazolc, it produces dose - dependent acid - suppression.
- In erosive esophagitis PPIs cause healing in 85%. In 10% of cases and in extraesophageal complications doses may be given twice daily for 3 months.

5. Zollinger - Ellison syndrome: Drugs of 1st choice.

6. Chronic idiopathic urticaria:

Caused by H pylori. Lansoprazole is given combined with amoxicillin.

7. Immunomodulator: They inhibit several leukocyte functions, reduce killer cell cytotoxicity, chemotaxis and superoxide anion generation.

Dose : orally as capsules, once daily, in the morning. Also twice daily in severe cases.

Omeprazole : 20 & 40 mg.

Lansoprazole: 30 mg.

Pantoprazole: 40mg.

Rabeprazole : 20 mg.

PPIs are given 30 - 60 minutes before breakfast, but pantoprazole may be given before, during or after breakfast.

- Also by repeated IVI or IV infusion.

Adverse effects

Duration & dose - dependent:

1. Recurrence: less than H2 antagonists.

2. Hypochlorhydria:

More than H2 antagonis •

Long term use ↓Hcl → colonization of stomach by bacteria (intestinal dysbiosis) → reduction of salivary or dietary nitrates to nitrites → carcinogenic nitroso compounds.

Also ↑gastrin → ↑cell growth. This → malignancy.

3. ↑ GIT bacteria → ↑risk of community - acquired & nosocomial respiratory infections and also GIT infections.

4. Long term PPIs decrease absorption of vitamin B12, iron and calcium causing their deficiency.

This may cause hip, wrest & spine fracture. So, give calcium supplement.

5. Enzyme inhibition: more significant clinically by omeprazole.

6. Diarrhea, abdominal pain, nausea & vomiting.

7. Headache, dizziness & asthenia.

H2 antagonists

1. Ranitidine.
2. Famotidine.
3. Nizatidine.

Mechanism

A) Acid suppression:

H2 receptors are linked via Gs proteins to adenyl cyclase.

H2 antagonists are reversible competitive H2 blockers decreasing intracellular cAMP particularly in parietal cells.

↓Hcl secretion mediated by histamine completely and by Ach & gastrin partially.

Marked reduction in fasting and nocturnal acid secretion (main effect) and less reduction in meal stimulated and day time acid secretion (duration of secretion inhibition is 12 hours). In a linear dose - dependent manner.

Efficacy is higher when given twice daily than once daily even if we double the once daily dose.

B) H pylori suppression by ranitidine.

Famotidine is more potent than ranitidine, but ranitidine has higher efficacy due to H pylori suppression.

Pharmacokinetics

Rapid absorption orally.

Peak effect: 2 hours.

Nizatidine has high (100%) oral bioavailability but the other H2 blockers have low bioavailability. 50% of ranitidine has 1st pass metabolism and 50% of famotidine is decomposed by acid.

So, famotidine is used in liver diseases and ranitidine in patients with delayed gastric emptying.

Plasma t1/2 is 3 hours.

Not cumulative.

Clearance is mainly renal (affected by renal diseases). Also hepatic. CL is decreased in up to 50% of old patients.

Due to non specificity of cimetidine (the 1st H2 blocker), its use is markedly decreased to avoid its more frequent and more severe adverse effects.

USES

1. DU:

A. Short term (acute therapy) leads to healing rate of 70% (4 weeks therapy) and 90% (8 weeks).

Oral dose: ranitidine & nizatidine 150 mg and famotidine 20 mg in the morning and at bed time. Total dose may be given at bed time but efficacy is reduced.

B. Maintenance therapy: only bed time dose for 1-5 years.

2. GU:

Less effective because there is normal or low Hcl. So there is lower healing rate and healing is delayed than DU by 2-4 weeks. Also in acute gastritis and gastric erosion e.g. by NSAIDs.

3. GERD:

In GERD, 50% have erosive esophagitis. H2 antagonists cause healing in 50%.

Low healing rates and recurrence rate is higher than PU.

4. Functional possibly acid - related dyspepsia. Small dose for short period.

5. Stress ulcer: IV injection or infusion is preferred.

6. GIT bleeding.

7. Before anesthesia in e.g. cesarean section to avoid aspiration pneumonia (Mendelson's syndrome).

- Ranitidine is used in combination therapy for H pylori.
- H2 blockers can be given by slow IV injection or infusion in acute and severe cases.
- Because H2 antagonists have less efficacy than proton pump inhibitors they are second choice in GERD and severe PU.

Adverse effects

A) Caused by all H2 antagonists:

1.Tolerance due to up regulation of H2 receptors and rebound hyperacidity.

2. Recurrence on withdrawal.

3. Hypochlorhydria: ……

This adverse effect is much more significant by PPIs.

4. Rapid IV injection may cause decrease cardiac output, arrhythmias or heart block.

B) Caused more by ranitidine:

1. CNS manifestations, specially in old patients: confusion, hallucination, insomnia and depression.
2. Impotence and loss of libido, gynecomastia and galactorrhea (weak antiandrogen).
3. Enzyme inhibition.

C) Caused by famotidine:

1. Diarrhea.
2. Bronchial asthma.
3. Headache.

D) Caused by nizatidine:

1. Cholinergic effects: Lacrimation, salivation, emesis, miosis & diarrhea.
2. Mild increase in serum cholesterol and uric acid.