Lecture 5
GIT Disorders

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DRUGS USED TO TREAT PEPTIC ULCER DISEASE AND GASTROESOPHAGEAL REFLUX DISEASE.

- The two main causes of peptic ulcer disease are infection with gram-negative Helicobacter pylori and the use of nonsteroidal anti-inflammatory drugs (NSAIDs). Increased hydrochloric acid (HCl) secretion and inadequate mucosal defense against gastric acid also play a role. Treatment approaches include 1) eradicating the H. pylori infection, 2) reducing secretion of gastric acid with the use of PPIs or H2-receptor antagonists, and/or 3) providing agents that protect the gastric mucosa from damage, such as *misoprostol* and *sucralfate*.

1.H2-receptor antagonists and regulation of gastric acid secretion.

- By competitively blocking the binding of histamine to H2 receptors, these agents reduce the secretion of gastric acid.
- The four drugs used in the United States—*cimetidine* , *ranitidine* , *famotidine* , and *nizatidine* —potently inhibit (greater than 90%) basal, food-stimulated, and nocturnal secretion of gastric acid.
- *Cimetidine* was the first histamine H2-receptor antagonist. However, its utility is limited by its adverse effect profile and drug–drug interactions.
- **Therapeutic uses:** The use of these agents has decreased with the advent of PPIs.

- **a. Peptic ulcers:** All four agents are equally effective in promoting the healing of duodenal and gastric ulcers. However, recurrence is common if H. pylori is present and the patient is treated with these agents alone. Patients with NSAID-induced ulcers should be treated with PPIs, because these agents heal and prevent future ulcers more effectively than H2 antagonists do.
- **b. Acute stress ulcers:** These drugs are given as an intravenous infusion to prevent and manage acute stress ulcers associated with high-risk patients in intensive care units. However, because tolerance may occur with these agents in this setting, PPIs have gained favor for this indication.

- **c. Gastroesophageal reflux disease (GERD):**

Low doses of H2, are effective for the treatment of heartburn (GERD) in only about 50% of patients. H2-receptor antagonists act by stopping acid secretion. Therefore, they may not relieve symptoms for at least
45 minutes. Antacids more quickly and efficiently neutralize stomach acid, but their action is only temporary. For these reasons, PPIs are now used preferentially in the treatment of GERD, especially for patients with severe heartburn.

Pharmacokinetics:

After oral administration, the H2 antagonists distribute widely throughout the body (including into breast milk and across the placenta) and are excreted mainly in urine. *Cimetidine*, *ranitidine,* and *famotidine* are also available in intravenous formulations. The half-life of all of these agents may be increased in patients with renal dysfunction, and dosage adjustments are needed.

Adverse effects:

- In general, the H2 antagonists are well tolerated. *Cimetidine* can have endocrine effects. These effects include gynecomastia and galactorrhea (continuous release/discharge of milk).
- *Cimetidine* inhibits several cytochrome P450 isoenzymes and can interfere with the metabolism of many other drugs, such as *warfarin.* All H2 antagonists may reduce the efficacy of drugs that require an acidic environment for absorption, such as *ketoconazole.*

2. PPIs: Proton Pump Inhibitors.

- The available PPIs include *esomeprazole, lansoprazole omeprazole, pantoprazole* and *rabeprazole*. *Omeprazole, esomeprazole*, and *lansoprazole* are available over-the counter for short-term treatment of GERD.

Actions: These agents are prodrugs with an acid-resistant enteric coating to protect them from premature degradation by gastric acid. At standard doses, PPIs inhibit both basal and stimulated gastric acid secretion by more than 90%.

Therapeutic uses: The PPIs are superior to the H2 antagonists in suppressing acid production and healing ulcers. Thus, they are the preferred drugs for stress ulcer treatment and prophylaxis and for the treatment of GERD,

- If an H2-receptor antagonist is needed, it should be taken well after the PPI, because H2 antagonists reduce the activity of the proton pump.

- **Pharmacokinetics:**

All of these agents are effective orally. Formmaximum effect, PPIs should be taken 30 to 60 minutes before breakfast or the largest meal of the day.

- 3. **Antacids**

Antacids are weak bases that react with gastric acid to form water and a salt to diminish gastric acidity. Because pepsin (a proteolytic enzyme) is inactive at a pH greater than 4, antacids also reduce pepsin activity.

Therapeutic uses:

Antacids are used for symptomatic relief of peptic ulcer disease and GERD, and they may also promote healing of duodenal ulcers. They should be administered after meals for maximum effectiveness**.**

- **Adverse effects:**

Aluminum hydroxide tends to cause constipation, whereas *magnesium hydroxide* tends to produce diarrhea. Preparations that combine these agents aid in normalizing bowel function. Absorption of the cations from antacids (Mg^{2+}, Al^{3+}, Ca^{2+}) is usually not a problem in patients with normal renal function; however, accumulation and adverse effects may occur in patients with renal impairment.

- Thanks For listining