Drugs Used in the Treatment of Gastrointestinal Diseases

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Drugs Used for GI Diseases

- Drugs Used in Acid-Peptic Diseases
- Drugs Stimulating GI Motility
- Laxatives
- Antidiarrheal Agents
- Drugs for Irritable Bowel Syndrome
- Antiemetic Agents
- Drugs Used to Treat Inflammatory Bowel Disease
- Pancreatic Enzyme Supplements (Digestives)
Acid-Peptic Diseases

- Gastroesophageal reflux
- Peptic ulcer (gastric and duodenal)
- Stress-related mucosal injury

Pathogenesis:

Aggressive Factors

- Acid, Pepsin
- Bile salts
- Drugs (NSAIDs)
- H. pylori

Defensive Factors

- Mucus secretion
- Bicarbonate secretion
- Blood flow
- Processes of restitution and regeneration after cellular injury
- Prostaglandins
Physiology of Acid Secretion

• Parietal cell contains receptors for gastrin (CCK-B), histamine (H₂), and acetylcholine (M₃).

• Activation of theses receptors ➤ acid secretion from H⁺/K⁺ ATPase (proton pump) on canalicular surface.
Physiology of Acid Secretion

• In close proximity to parietal cells are gut endocrine cells called **enterochromaffin-like (ECL) cells**.

• ECL cells synthesize and secrete **histamine**.

• ECL cells also have receptors for **gastrin** and **acetylcholine**, which stimulate histamine release.

• Histamine binds to **H₂ receptor** on the parietal cell → ↑ cAMP and stimulate acid secretion by the **H⁺/K⁺ ATPase**.
Drugs Used in Acid-Peptic Diseases: Antiulcerants

1. Agents that Reduce Intragastric Acidity:
   - Antacids
   - H2-receptor antagonists
   - Proton pump inhibitors

2. Mucosal Protective Agents:
   - Sucralfate
   - Prostaglandin Analogs
   - Bismuth Compounds

3. Anti-Helicobacter pylori drugs
1. Agents that Reduce Intragastric Acidity:

**Antacids**

- Sodium bicarbonate
- Calcium carbonate
- Magnesium hydroxide *SUSP*
- Aluminum hydroxide *TAB, SUSP*
- Aluminium/Mg (Aluminum and Magnesium hydroxide) *TAB, SUSP*
- Aluminium/Mg/S (Simethicone) *TAB, SUSP*

- Antacids have been used for centuries in treatment of dyspepsia and acid-peptic disorders.
Antacids

- Weak bases that are react with gastric hydrochloric acid to form a salt and water $\rightarrow \downarrow$ intragastric acidity.
After a meal, approximately 45 mEq/h of HCl is secreted.

A single dose of 156 mEq of antacid 1 hr after a meal effectively neutralizes gastric acid for up to 2 hr.

Acid-neutralization capacity depending on:

- Rate of dissolution (tablet versus liquid)
- Water solubility
- Rate of reaction with acid
- Rate of gastric emptying
Antacids

Sodium bicarbonate (baking soda)
• reacts rapidly with HCl to produce CO$_2$ + NaCl.
• **Adverse effects:** distention and belching, *metabolic alkalosis* in high doses or in patients with renal insufficiency, *fluid retention* in heart failure, HTN, and renal insufficiency.

Calcium carbonate
• Less soluble and reacts more slowly than sodium bicarbonate with HCl to form CO$_2$ + CaCl$_2$.
• may cause belching, hypercalcemia, renal insufficiency and metabolic alkalosis (*milk-alkali syndrome*) in excessive doses.
• used for a number of other indications apart from its antacid properties.
Antacids

Magnesium hydroxide (Milk of magnesia)

Aluminum hydroxide

- react slowly with HCl to form MgCl\(_2\) or AlCl\(_3\) + water.
- No gas is generated → No belching occurs.
- Metabolic alkalosis is also uncommon.
- Unabsorbed Mg salts may cause osmotic diarrhea and Al salts may cause constipation ➤ administered together in formulations: Aluminium/Magnesium
- Both Mg and Al are absorbed and excreted by kidneys → should not be used for long-term in renal insufficiency.
Antacids

All may affect absorption of other medications:
- By binding the drug (reducing its absorption)
- By increasing intragastric pH so that the drug's dissolution
- By altering solubility (especially weakly basic or acidic drugs)

► Should not be given within 2 hours of doses of tetracyclines, fluoroquinolones, itraconazole, and iron.
1. Agents that Reduce Intragastric Acidity:

**H$_2$-receptor antagonists**

H2 blockers were the most commonly prescribed drugs from 1970s until the early 1990s.

**Relative potency**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Relative Potency</th>
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<tr>
<td>Cimetidine</td>
<td>1</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>4-10</td>
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<tr>
<td>Nizatidin</td>
<td>4-10</td>
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<tr>
<td>Famotidine</td>
<td>20-50</td>
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H$_2$-receptor antagonists: Dosage Forms

- **Cimetidine**: *Tab 200, Syrup 200 mg/5ml, Amp 100 mg/ml, 2ml*
- **Ranitidine**: *Tab, Cap 150, 300, Effervescent Tab 300, Amp 25, 50 mg/ml, 2ml, Oral Solution 75mg/5ml*
- **Famotidine**: *Tab 20, 40, Amp 20 mg/ml*
H$_{2}$-receptor antagonists:

- Highly selective and competitive inhibition at the parietal cell H$_{2}$ receptor
- ↓Volume of gastric secretion and concentration of pepsin
- ↓Acid secretion stimulated by histamine and by gastrin and cholinomimetic agents
H\textsubscript{2}-Receptor Antagonists

- Undergo \textit{first-pass hepatic} metabolism → bioavailability of \(~50\%\) except for Nizatidine

- Cleared by a combination of hepatic metabolism, glomerular filtration, and renal tubular secretion.

- Commonly given twice daily.

- Especially effective at inhibiting \textit{nocturnal acid secretion} (which depends largely on histamine).
H$_2$-receptor antagonists:

**Clinical Uses:**

- Gastroesophageal Reflux Disease (GERD)
- Peptic Ulcer Disease
- Dyspepsia (OTC)
- Prevention of Bleeding from Stress-Related Gastritis
H$_2$-receptor antagonists: Adverse Effects

- extremely safe drugs (< 3%)
- i.v. administration → ↑ risk of pneumonia in critically ill patients
- i. v. Cimetidine → Mental status changes (confusion, hallucinations, agitation) especially in elderly patients in ICU or with renal or hepatic dysfunction.
- Cimetidine inhibits binding of dihydrotestosterone to androgen receptors, inhibits metabolism of estradiol, and increases serum prolactin levels: long-term use or in high doses → gynecomastia or impotence in men and galactorrhea in women.
- Rapid i.v. infusion → bradycardia and hypotension (blockade of cardiac H$_2$ receptors)
**H₂-receptor antagonists: Drug Interactions**

- **Cimetidine** inhibits CYP1A2, CYP2C9, CYP2D6, and CYP3A4 → \( \uparrow \) half-lives of drugs metabolized by these pathways.

- Ranitidine binds 4–10 times less avidly than cimetidine to cytochrome P450.

- Negligible interaction occurs with nizatidine and famotidine.
1. Agents that Reduce Intragastric Acidity: Proton pump inhibitors (PPIs)

- **H⁺/K⁺ ATPase inhibitors**: the most widely prescribed drugs worldwide due to their efficacy and safety.

  - **Omeprazole**: racemic mixture of R- and S-isomers
  - **Esomeprazole**: S-isomer of omeprazole
  - **Lansoprazole**
  - **Pantoprazole**
  - **Rabeprazole**
Proton pump inhibitors (PPIs): Dosage forms

- **Omeprazole:** Delayed Release Cap (20mg), Powder for Oral Suspension
- **Esomeprazole:** Delayed Release Cap, Tab (20, 40mg)
- **Lansoprazole:** Delayed Release Cap (15, 30mg)
- **Pantoprazole:** Delayed Release Cap (15, 20, 40mg), Delayed Release Tab (20, 40mg), Inj Vial 40mg
- **Rabeprazole:** Delayed Release Tab (20mg)
Proton Pump Inhibitors (PPIs)

- **MOA:** In contrast to H$_2$ antagonists, inhibit both fasting and meal-stimulated secretion *because of blocking final common pathway of acid secretion.*

- Inhibit 90–98% of 24-hr acid secretion.

- To protect drug from acid degradation → formulated for delayed release as acid-resistant, enteric-coated cap or tab.
Proton Pump Inhibitors

• PPIs are **inactive prodrugs**.

• PPIs are **lipophilic weak bases** and after intestinal absorption diffuse readily into **acidified compartments** (parietal cell) → concentrated more than **1000-fold** by Henderson-Hasselbalch trapping.

• Then PPIs are rapidly converted to active form, which forms a covalent disulfide bond with $H^+, K^+$ ATPase, **irreversibly** inactivating the enzyme.
Proton Pump Inhibitors (PPIs)

- ↓Bioavailability (~50%) by food → should be administered 1 hr before a meal (usually breakfast).
- PPIs have a short serum half-life (1.5 hrs) but acid inhibition lasts up to 24 hrs.
- At least 18 hours are required for synthesis of new H\(^+\),K\(^+\) ATPase pump molecules.
- Up to 3–4 days are required for full acid-inhibition.
- PPIs undergo rapid first-pass hepatic metabolism.
Proton Pump Inhibitors (PPIs)

From a pharmacokinetic perspective, PPIs are *ideal drugs*:

- They have a short serum half-life
- They are concentrated on their site of action
- They are activated near their site of action
- They have a long duration of action
Proton Pump Inhibitors (PPIs): Clinical Uses

- Gastroesophageal Reflux Disease (GERD)
- Peptic Ulcer Disease
  - *H pylori*-Associated Ulcers
  - NSAID-Associated Ulcers
  - Prevention of Rebleeding from Peptic Ulcers
- Nonulcer Dyspepsia
- Prevention of Stress-Related Mucosal Bleeding
- Gastrinoma and Other Hypersecretory Conditions
Proton Pump Inhibitors (PPIs): Adverse Effects

- PPIs are extremely safe.
- A minor ↓cyanocobalamin (Vit B₁₂) absorption
- A modest ↑risk of hip fracture (may reduce calcium absorption or inhibit osteoclast function)
- ↑Risk of respiratory and enteric infections
- ↑Serum Gastrin → hyperplasia of ECL cells
- ↓Gastric Acidity → ↑chronic inflammation in the gastric body among patients infected with *H pylori* → ↑risk factors for gastric adenocarcinoma
Proton Pump Inhibitors (PPIs): Drug Interactions

- ↓Absorption of drugs for which intragastric acidity affects drug bioavailability (ketoconazole, itraconazole, digoxin)

- Omeprazole may inhibit metabolism of warfarin, diazepam, phenytoin and clopidogrel.
2. Mucosal Protective Agents

• Mucus and epithelial cell-cell tight junctions restrict back diffusion of acid and pepsin.
• Mucosal prostaglandins are important in stimulating mucus and bicarbonate secretion and mucosal blood flow.

• Sucralfate
• Prostaglandin Analogs
• Bismuth Compounds
2. Mucosal Protective Agents

Sucralfate

- *Tab 1 g, Powder for Suspension 1 g/sachet*
- A salt of sucrose complexed to sulfated aluminum hydroxide.
- In water or acidic solutions it forms a viscous, tenacious paste that *binds selectively to ulcers* for up to 6 hrs.
- Less than 3% of intact drug and Al is absorbed from intestinal tract; remainder is excreted in feces.

- Precise *MOA* is unclear: *negatively charged sucrose sulfate* binds to *positively charged proteins* in the base of ulcers or erosion, *forming a physical barrier* and *stimulates mucosal PGs and bicarbonate secretion*.
Sucralfate

Clinical Uses:
• 1 g QID on an empty stomach (at least 1 hr before meals)
• For prevention of stress-related bleeding without increase the risk of pneumonia.

Adverse Effects:
• No systemic adverse effects.
• Constipation in 2% of patients
• Should not be used for long periods in renal insufficiency (because a small amount of Al is absorbed).
2. Mucosal Protective Agents

Prostaglandin Analogs: Misoprostol

- **Tab 100, 200 mcg**
- Analog of PGE1
- Serum half-life is <30 min → must be administered 3–4 times daily. It is excreted in the urine.

**MOA:**
- Stimulates mucus and bicarbonate secretion
- Enhances mucosal blood flow
- It binds to a PG receptor on parietal cells → ↓ histamine-stimulated cAMP production and causing modest acid inhibition.

- **Other actions:** stimulation of intestinal electrolyte and fluid secretion, intestinal motility, and uterine contractions.
Misoprostol

**Clinical Uses:**

- Approved for prevention of NSAID-induced ulcers in high-risk patients

**Adverse Effects:**

- Diarrhea and cramping abdominal pain
- Uterine contractions → *should not be used during pregnancy or in women of childbearing potential*
2. Mucosal Protective Agents

**Bismuth Compounds**

- **Bismuth subsalicylate** (OTC in the world)
- **Bismuth subcitrate** *Tab 120mg, in Iran*
- Bismuth subsalicylate undergoes rapid dissociation within stomach.
- Over 99% of bismuth appears in stool.

**Adverse Effects:**

- They have excellent safety profiles.
- Harmless blackening of the stool.
- Should be used for short periods only.
- High dosages of bismuth subsalicylate may lead to salicylate toxicity.
**Bismuth Compounds**

Precise **MOA** of bismuth is unknown:

- Bismuth coats ulcers, creating a protective layer
- Bismuth stimulates PG, mucus, and bicarbonate secretion.
- Bismuth subsalicylate reduces stool frequency and liquidity in acute infectious diarrhea (due to salicylate inhibition of intestinal prostaglandin and chloride secretion).
- Bismuth has direct antimicrobial effects and binds enterotoxins.
- Bismuth compounds have direct antimicrobial activity against *H pylori*. 
Bismuth Compounds

Clinical Uses

- Nonspecific treatment of dyspepsia and acute diarrhea (Bismuth subsalicylate)
- Prevention of traveler's diarrhea (Bismuth subsalicylate)
- Eradication of *H pylori* infection (Bismuth subcitrate) as quadruple therapies (second-line therapies)
Agents Used in infection of Helicobacter Pylori

- Triple therapy regimens (first-line therapy): PPI + Clarithromycin + Amoxicillin or Metronidazole BID for 14 days)

- Quadruple therapies (second-line therapies) PPI BID + Bismuth subcitrate 140 mg + Metronidazole 125 mg + Tetracycline 125 mg QID for 10 days.
Drugs Stimulating Gastrointestinal Motility: Prokinetic agents

- Drugs that can selectively stimulate gut motor function.
- Agents that increase lower esophageal sphincter pressures may be useful for GERD.
- Drugs that improve gastric emptying may be helpful for gastroparesis and postsurgical gastric emptying delay.
- Agents that stimulate small intestine may be beneficial for postoperative ileus or chronic intestinal pseudo-obstruction.
- Agents that enhance colonic transit may be useful in treatment of constipation.
Drugs Stimulating Gastrointestinal Motility

- Cholinomimetic Agents
- Metoclopramide & Domperidone
- Macrolides
- Laxatives
- Chloride Channel Activator
- Opioid Receptor Antagonists
- Serotonin 5-HT₄-Receptor Agonists
Physiology of the Enteric Nervous System

ENS is organized into 2 plexi:

1. **Submucosal plexus:** interconnected networks of ganglion cells and nerve fibers mainly located in submucosa

2. **Myenteric plexus:** between the circular and longitudinal muscle layers
Physiology of the Enteric Nervous System

• Release of serotonin (5-HT) from intestinal mucosa enterochromaffin (EC) cells stimulates:
  • 5-HT3 receptors stimulating nausea, vomiting, or abdominal pain.
  • 5-HT4 receptors enhance release of ACh.

• Dopamine acts as an inhibitory neurotransmitter in GI tract, decreasing intensity of esophageal and gastric contractions.
Drugs Stimulating Gastrointestinal Motility:

**Cholinomimetic Agents**

**Bethanechol**
- Stimulates muscarinic M3 receptors on muscle cells and at myenteric plexus synapses.
- It was used in the past for treatment of GERD and gastroparesis.

**Neostigmine**
- An Acetylcholinesterase inhibitor which can enhance gastric, small intestine, and colonic emptying.
  - i.v neostigmine → treatment of hospitalized patients with acute large bowel distention
  - *Cholinergic effects* include excessive salivation, nausea, vomiting, diarrhea, and bradycardia.
Drugs Stimulating Gastrointestinal Motility

**Metoclopramide & Domperidone**

- Dopamine $D_2$ receptor antagonists → primary prokinetic mechanism (activation of dopamine receptors inhibits cholinergic smooth muscle stimulation in GI)

- They increase esophageal peristaltic amplitude, increase lower esophageal sphincter pressure, and enhance gastric emptying but have no effect on small intestine or colonic motility.

- They also block $D_2$ receptors in chemoreceptor trigger zone of medulla → potent antinausea and antiemetic action.
Metoclopramide & Domperidone

Clinical Uses

- Gastroesophageal Reflux Disease
- Impaired Gastric Emptying
- Nonulcer Dyspepsia
- Prevention of Vomiting
- Postpartum Lactation Stimulation
Metoclopramide & Domperidone

**Adverse Effects**

- **Metoclopramide:**
- **CNS** (the most common): restlessness, drowsiness, insomnia, anxiety (10–20% of patients, especially elderly)
- **Extrapyramidal effects** (dystonias, akathisia, parkinson)
- **Tardive dyskinesia**, sometimes irreversible, has developed in prolonged use.
- *Long-term use should be avoided especially in the elderly.*
- ↑**Prolactin** levels (caused by metoclopramide and domperidone) → galactorrhea, gynecomastia, impotence, and menstrual disorders.
- **Domperidone** is extremely well tolerated (does not cross BBB to a significant degree).
Drugs Stimulating Gastrointestinal Motility

**Macrolides**

- **Erythromycin** directly stimulate motilin receptors on gastrointestinal smooth muscle and promote the onset of a migrating motor complex.

- Intravenous erythromycin is beneficial in some patients with gastroparesis; however, tolerance rapidly develops.

- It may be used in patients with acute upper gastrointestinal hemorrhage to promote gastric emptying of blood before endoscopy.