GIT Pharmacology

Antiulcer Drugs

Overview

Peptic Ulcer Disease (PUD) results from an imbalance between:

A. Aggressive factors

- Gastric acid (HCl)
- Pepsin
- *Helicobacter pylori*
- NSAIDs

B. Defensive factors

- Mucus
- Bicarbonate
- Prostaglandins
- Mucosal blood flow

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Mechanisms of Antiulcer Drugs

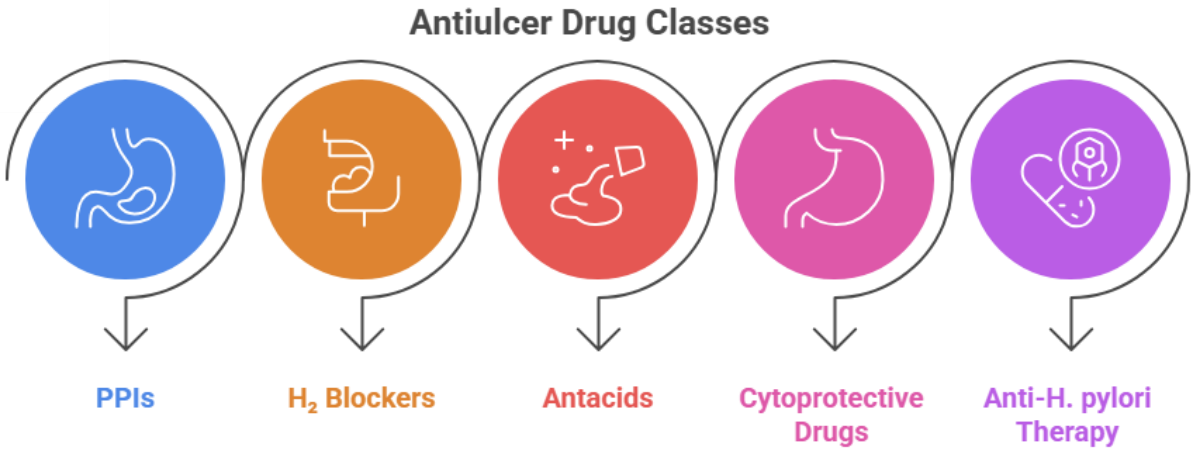
- **Antiulcer drugs act by:**
  - Reducing acid secretion
  - Enhancing mucosal protection
  - Eradicating *H. pylori*

Cellular Physiology of Acid Secretion

- Parietal cells in the stomach secrete HCl
- **Key receptors on parietal cells**
  - H_2 receptor (Histamine) → ↑ cAMP → activates proton pump
  - M_3 receptor (Acetylcholine) → ↑ Ca^{2+}
  - CCK-B receptor (Gastrin) → ↑ Ca^{2+}
- **Final step**
  - H^+/K^+ ATPase (Proton pump) → secretes H^+ into gastric lumen

Classes of Antiulcer Drugs & Molecular Mechanisms

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1. Proton Pump Inhibitors (PPIs)

Examples:

- Omeprazole, Pantoprazole

Mechanism of Action

1. Prodrugs absorbed in small intestine → reach parietal cells via blood
2. Diffuse into acidic secretory canaliculi
3. Protonated and converted to active sulfenamide form
4. Covalently bind to cysteine residues (Cys813, Cys822) on H^+/K^+-ATPase
5. Cause **irreversible inhibition** of proton pump
6. Block both basal and stimulated acid secretion (histamine, gastrin, ACh)

Resistance / Reduced Effectiveness

- CYP2C19 polymorphism → rapid metabolism
- Resynthesis of new proton pumps
- Improper timing (not taken before meals)
- Reduced activation in less acidic conditions
- In *H. pylori* therapy: antibiotic resistance affects outcomes

2. H_2 Receptor Blockers

Examples:

- Ranitidine, Famotidine

Mechanism of Action

1. Competitive antagonists at H_2 receptors on parietal cells
2. Block adenylate cyclase activation
3. Decrease cAMP levels
4. Reduce protein kinase A (PKA) activity

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5. Decrease H^+/K^+-ATPase activity
6. Mainly inhibit basal (nocturnal) acid secretion

Resistance / Tolerance

- Tachyphylaxis with prolonged use
- Upregulation of gastrin and acetylcholine pathways
- Increased histamine release
- Receptor desensitization

3. Antacids

Examples:

- Magnesium hydroxide, Aluminum hydroxide

Mechanism of Action

1. **Neutralize gastric HCl:**
   - $Mg(OH)_2 + 2HCl \rightarrow MgCl_2 + 2H_2O$
   - $Al(OH)_3 + 3HCl \rightarrow AlCl_3 + 3H_2O$
2. Increase gastric pH
3. Reduce pepsin activity (inactive at pH > 4)
4. Provide rapid symptomatic relief
5. Aluminum salts bind bile acids

Limitations

- No true resistance
- Short duration of action
- Acid rebound (more with calcium-containing antacids)
- Compensatory increase in acid secretion

4. Cytoprotective Drugs

A. Sucralfate

Examples:

- Sucralfate

Mechanism of Action

1. Polymerizes in acidic pH → forms viscous gel
2. Binds to ulcer base → protective barrier
3. Prevents back-diffusion of H^+
4. Inhibits pepsin locally

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5. Stimulates prostaglandin (PGE_2) production
6. Increases mucus and bicarbonate secretion
7. Promotes epithelial healing

Resistance / Limitations

- No true resistance
- Requires acidic environment
- Interferes with absorption of other drugs
- Does not suppress acid secretion

B. Misoprostol

Examples:

- Misoprostol

Mechanism of Action

1. Synthetic PGE_1 analog
2. Binds EP3 receptors on parietal cells
3. Inhibits adenylate cyclase → ↓ cAMP
4. Reduces acid secretion
5. Increases mucus and bicarbonate secretion
6. Enhances mucosal blood flow
7. Promotes epithelial repair

Resistance / Limitations

- No classical resistance
- Receptor desensitization
- Dose-limiting diarrhea
- Requires intact prostaglandin signaling

5. Anti–H. pylori Therapy

Examples:

- PPI + Clarithromycin + Amoxicillin

Mechanism of Action

a) PPI Component

1. Suppresses gastric acid
2. Increases gastric pH
3. Enhances antibiotic stability

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4. Promotes bacterial replication → increases susceptibility

b) Clarithromycin

1. Binds 50S ribosomal subunit (23S rRNA)
2. Inhibits translocation
3. Blocks protein synthesis

c) Amoxicillin

1. Binds penicillin-binding proteins (PBPs)
2. Inhibits peptidoglycan cross-linking
3. Causes bacterial cell lysis

Resistance

- **PPI:** CYP2C19 polymorphism, inadequate acid suppression
- **Clarithromycin:** 23S rRNA mutations, efflux pumps
- **Amoxicillin:** altered PBPs, β-lactamase, reduced permeability

Prokinetic Drugs

Overview

- Prokinetics are drugs that **increase gastrointestinal motility**.

Clinical Uses

- Gastroparesis
- GERD

Mechanism of GI Motility Control

- **Enteric neurotransmitters:**
  - Acetylcholine (ACh) → ↑ motility
  - Dopamine (D2) → ↓ ACh release → ↓ motility
  - Serotonin (5-HT4) → ↑ ACh release → ↑ motility

Classification of Prokinetic Drugs

1. Dopamine (D2) Receptor Antagonists

A. Metoclopramide

Cellular & Molecular MOA:

1. Antagonizes D_2 receptors on presynaptic enteric neurons.
2. Removes dopamine-mediated inhibition of acetylcholine (ACh) release.

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