Anti-ulcer Agents

Gastric juices: 2.5L secreted per day
- Chief cells → pepsinogens
- Parietal cells → HCl
- Enterochromaffin-like cells → histamine
- Mucus-secreting cells → mucus

\[ \text{H}_2, \text{ACh, gastrin} \rightarrow (+)\text{H}^+\text{K}^+\text{ATPase proton pump} \rightarrow \text{acid} \]
\[ \text{PGE}_2 + \text{PGI}_2 \rightarrow (-)\text{acid} + (+)\text{mucus} + \text{dilate mucosal blood vessels} \]

Peptic Ulcer Disease treatment

<table>
<thead>
<tr>
<th>Cause of damage</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>(H. \text{pylori} \text{ infection} )</td>
<td>Antibiotics + PPI or ( \text{H}_2 ) blocker</td>
</tr>
<tr>
<td>↑acid secretion</td>
<td>↓Acid by PPI, ( \text{H}_2 ) blockers, or prostaglandins</td>
</tr>
<tr>
<td>↓Mucus layer thickness</td>
<td>Prostaglandins &amp; sucralfate (+)mucus secretion</td>
</tr>
<tr>
<td>↓Bicarbonate</td>
<td>Prostaglandins &amp; sucralfate</td>
</tr>
<tr>
<td>↑Type 1 pepsin</td>
<td>↑Stomach pH, bind to Al antacids or sucralfate</td>
</tr>
<tr>
<td>↓Mucosal blood flow</td>
<td>Prostaglandins, sucralfate</td>
</tr>
<tr>
<td>NSAID-induced ulcer</td>
<td>Withdraw NSAID, use COX-2 selective agent + prostaglandin analogue</td>
</tr>
</tbody>
</table>

\( \downarrow \) Gastric acid secretion

- **\( \text{H}_2 \) blockers:** antagonism of histamine \( \text{H}_2 \) receptors
  - Agents (OTC): cimetidine, ranitidine, famotidine, nizatidine
  - Actions: \( \downarrow \)acid secretion, gastrin, pepsin, intrinsic factor secretion, \( \text{H}^+ \) concentration
  - \( \text{P}' \)kinetics: good po absorption, peak 1-2hr, duration 6-12hr, CYP450 metabolism (cimetidine >> others), renal elimination
  - Uses: promotes healing of ulcers, treats uncomplicated GERD, Zollinger-Ellison Syndrome
  - SE: cimetidine > others, overall low incidence, some are mediated by \( \text{H}_2 \) antagonist action
    - Common SE: nausea, diarrhea, constipation, headache, dizziness, pruritus, loss of libido/impotence, microorganisms from hypochloridic stomach, bradycardia (if rapid IV)
    - Cimetidine: sexual dysfunction, gynecomastia, CYP450 interactions, blood dyscrasias, hepatotoxicity, renal toxicity

- **PPIs:** inhibit \( \text{H}^+\text{K}^+\text{ATPase proton pump} \)
  - Agents: omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, pantoprazole
  - Prodrugs: requires acidic medium for activation
    - Active metabolite forms disulfide bridge with enzyme → irreversible inhibition
    - Enteric coat: prevents premature conversion in stomach, allows absorption in intestine
  - Pharmacokinetics: QD dosing, highly protein bound, highly metabolized by CYP450
  - Uses: treats ulcers, erosive esophagitis, GERD, Zollinger-Ellison syndrome (DOC), reflux esophagitis, NSAID-induced gastropathy
  - SE: headache, nausea, diarrhea, abdominal pain, rash, mucosal hyperplasia
    - Long term use ↑risk: hip fracture (pts >50y/o), infectious gastroenteritis, \( \text{C. diff} \) colitis
    - Interaction with clopidogrel: (−)CYP2C19 → can’t convert prodrug clopidogrel to active form (omeprazole >> pantoprazole)

- **Antimuscarinics** \( (M_1 \text{ & } M_3) \): need high doses to suppress just 50% of gastric secretion
  - CNS active agents: atropine, scopolamine
  - CNS inactive agents: probantheline, methscopolamine, glycopyrrolate
  - MOA: blocks \( M_1 \) (paracrine cells) & \( M_3 \) (parietal cells) cholinergic receptors
  - Efficacy: does not completely inhibit acid secretion, least effective, considered as anticholinergic SE
  - SE: tachycardia, constipation, blurred vision
    - If crosses BBB (CNS active): sedation, memory disruption, disorientation, psychosis
**Prostaglandin E derivatives**
- **Agent:** misoprostol
- **MOA:** (-)adenyl cyclase → (-)cAMP synthesis → (-)acid secretion; also (+)mucus secretion
- **Use:** used in combination with NSAIDs to prevent ulcer formation
- **SE:** GI cramping, diarrhea, uterine contractions

**Neutralize excess gastric acid: antacids**
- **Agents:** NaHCO₃, CaHCO₃, MgOH, ALOH, Mg trisilicate, Al trisilicate
- **Activity:** neutralizes intragastric HCl, ↑pH in stomach, ↓acid load to duodenum, ↓pepsin activity
- **Cations → soluble salts → absorbed in small intestines**
- **Divalent cations → poorly soluble salts → excreted in feces**
- **Mg & Al → interact with fatty acids → form soaps**
- **Systemic antacids:** absorbed into bloodstream, may ↑blood pH, alkalinate urine
- **Therapeutic uses:** heartburn, duodenal & peptic ulcers, erosive gastritis
- **Interactions:** bivalent & trivalent cations ↓absorption of ferrous salts, tetracyclines, quinolones, bile acids

**Repair mucosal barrier breakdown: cytoprotectants**
- **Agent:** sucralfate (basic aluminum-sucrose-sulfate)
- **MOA:** at pH <4 → polymerizes to form viscous gel → forms protective layer on ulcer surface → protects against HCl, pepsin, bile
  - Also: (-)pepsin activity and absorbs bile acids
- **Pharmacokinetics:** poorly absorbed from GI tract, duration 6-12hr
- **Uses:** enhances ulcer healing, comparable efficacy to H₂ blockers
- **SE:** constipation, binds other drugs (e.g. tetracycline), aluminum accumulation if renal impairment

**Prostaglandin-stimulated cytoprotection**
- **Prostaglandin analogs**

**Eradicate H. pylori**
- **Antimicrobial cocktail regimens**
  - **1st line:** PPI bid + amoxicillin 1g bid + clarithromycin 500mg bid → 14 days
  - **2nd line_a:** PPI bid + Pepto-Bismol 120mg qid + metronidazole 400mg tid + tetracycline 500mg tid → 10 days
  - **2nd line_b:** PPI bid + amoxicillin 1g bid + moxifloxacin 800mg qd → 10 days
- **Bismuth subsalicylate:** binds to ulcer base; ↑secretion of prostaglandin, mucus, and bicarb; ↓H. pylori