H₂ block | Histamine Receptor Antagonists

- **Agents:** cimetidine (Tagamet), ranitidine (Zantac), famotidine (Pepcid), nizatidine (Axid)
- **Histamine structure**
  - Two pKa’s: aliphatic pKa 9.4 + aromatic pKa 5.8
  - Equilibrium of two tautomeric structures: Nτ (aqueous) + Nτ (crystal salt)
    - Nτ tautomer is required for binding to H₂ receptors
  - Hydrophilic molecule
- **Biosynthesis**
  - L-histidine → histamine by two enzymes: L-histidine decarboxylase (specific, Vit B6 cofactor) or L-aromatic amino acid decarboxylase (non-specific)
  - Degraded by two pathways: N1-methylation + MAO oxidation or nonspecific oxidative deamination
- **Histamine receptors:** four types
  - H₁ → allergies
    - H₁ antagonist: basic nitrogen group (binds to anionic binding site) + 2 aromatic groups
    - Second generation H₁ antagonists: terfenadine, astemizole, fexofenadine, cetirizine
    - 2 hydroxy groups → ↑water solubility + ↓BBB penetration → ↓CNS sedation
    - Bulky groups on basic nitrogen → (−)binding to anionic site of M receptor → ↓anti-ACh effects
  - H₂ → stomach acid secretion
    - Compared to H₁: H₂ antagonists are ↑hydrophilicity (↓CNS effects) and do not have anti-ACh effects
  - H₃ → CNS effects e.g. antiepileptic and attention
  - H₄
- **Cimetidine SAR**
  - Substituted guanidine: guanidine group binds through bidentate bond to hydrophobic pocket
  - Nitrile group: -e- withdrawing group attracts e- from guanidine making it less basic → less protonated under physiological conditions → free to form bidentate bonds
  - Imidazole ring: binds well to histamine receptors, ↑affinity for receptor but is not essential
    - SE caused by imidazole ring: liver enzyme inhibition, antiandrogenic properties
    - Can replace imidazole ring with other aromatic/heteroaromatic groups to ↓SE
  - Methyl & thiomethylene groups: stabilize Nτ tautomer structure to ensure potency
- **Ranitidine, famotidine, nizatidine > cimetidine**
  - ↑Binding of basic moiety to receptors → ↑potency
  - Nizatidine: bioavailability not affected by concurrent antacid administration

PPIs | Proton Pump Inhibitors

- **Agents:** omeprazole (Prilosec), lansoprazole (Prevacid), pantoprazole (Protonix), rabeprazole (Aciphex), esomeprazole (Nexium), dexlansoprazole (Dexilant)

<table>
<thead>
<tr>
<th>Omeprazole</th>
<th>Lansoprazole</th>
<th>Esomeprazole</th>
<th>Pantoprazole</th>
<th>Rabeprazole</th>
<th>Dexlansoprazole</th>
</tr>
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<tbody>
<tr>
<td>1° PPI; liver enzyme inhibitor</td>
<td>Racemate of omeprazole; liver enzyme inhibitor</td>
<td>S-isomer of esomeprazole, better control of intragastric pH</td>
<td>Most potent PPI</td>
<td>Faster onset of action</td>
<td>Dual delayed release: fast (1-2hr) + slow (4-5hr)</td>
</tr>
</tbody>
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- **Prodrugs:** weak bases that require activation in acid environment
  - Enteric coated: prevents degradation in stomach → slower release
  - Also available as IV formulations
- **MOA:** irreversibly inhibit H⁺/K⁺ ATPase of the proton pump in the acid secretory pathway
  - Irreversible inhibition → body needs to re-synthesize new pumps → long duration of action
- **Revaprazan (in clinical trials):** reversible H⁺K⁺ ATPase inhibitor that binds K⁺ binding site of proton pump, rapid onset

PGE₂ Analogues | Stable Prostaglandin Analogues

- **Agents:** misoprostol (Cytotec), enprostil (Gardrin), ornoprostil (Allca, Ronok), benexate (Lonmiel)
  - Carboprost, sulprostone: abortificients
  - Latanoprost (Xalatan): anti-glaucoma agent to treat IOP
- **Biosynthesis of prostanoids:** synthesized from arachidonic acid via two COX enzymes
• Prostanoid receptors: 9 total
  o 3 types coupled to mobilization of intracellular Ca → inflammation, uterine stimulation, IOP, platelet aggregation
  o 5 types coupled to ↑cAMP levels → bronchodilation, antiplatelet aggregation, cytoprotection
  o 1 type associated with ↓cAMP accumulation → cytoprotective, antisecretory, uterine stimulation

• Misoprostol: cytoprotective properties
  o MOA: (+)EP3 receptors \( \rightarrow \) (–)cAMP formation \( \rightarrow \) (–)Ca & HCl release from parietal cell
  o Pharmacokinetics: rapidly absorbed & metabolized to active free acid
  o SE: diarrhea (EP1 or EP3 mediated), uterine contraction (EP3 mediated)

• Enprostil:
  o more potent at EP3 receptors than misoprostol, greater affinity at EP1 receptors

• Benexate (Japan only):
  o cytoprotective but non-prostaglandin-like, treats ulcers induced by indomethacin or stress

**Gastric Antagonists**

• Gastrointestinal peptidic hormone that stimulates gastric secretion
  o Vagal stimulation + gastrin \( \rightarrow \) (+)histamine release from enterochromaffin-like cells

• S-0509:
  o novel gastrin receptor antagonist that enhances healing of ulcers and has antisecretory effects

• Theoretical acid secretion control was shown to lose clinical efficacy after just a few days

**Somatostatin Analogues**

• 14 aa peptide release in GI tract and pancreas from paracrine cells, D-cells, enteric nerves, & hypothalamus
  o Many inhibitory actions: (–)gastric acid secretion, pepsinogen secretion, gastrin, motilin, etc.
  o Pharmacokinetics: very short plasma t½ due to degradation by peptidases
  o Octreotide (Sandostatin): analogue of somatostatin that is more metabolically stable
    o Treats acromegaly, neutralizes pH, treats esophageal variceal bleeding

**Antimicrobial Agents | H. pylori**

• H. pylori: gram negative bacteria that uses urease to prosper in highly acid stomach
  o Urease: breaks down urea to NH₃ + CO₂ \( \rightarrow \) ↓ acidity
  o Microaerophilic: likes low oxygen environments
  o Develops resistance quickly \( \rightarrow \) need a cocktail of agents and ↑ferredoxin

• Antimicrobial agents:
  o metronidazole, amoxicillin, tetracycline, macrolides (clarithromycin, azithromycin, erythromycin)
  o Metronidazole: active against most anaerobic bacterial infections
    o Microbial reduction of CS nitro group \( \rightarrow \) forms labile & chemically reactive intermediates \( \rightarrow \) intermediates covalently bind to DNA \( \rightarrow \) triggers lethal effect
  o Considered a prodrug because requires metabolic activation
  o Flavoproteins catalyze reduction of aromatic nitro group to amine

**Prokinetic Agents**

• Enhances GI motility & transit: ↓esophageal sphincter pressure in GERD, ↑gastric emptying, stimulate small intestine

• Dopamine D2 receptor antagonists
  o Agents: metoclopramide (Reglan), domperidone (Motilium)
  o MOA: 5-HT4 receptor agonism, central 5-HT3 receptor antagonism, dopamine receptor antagonism
  o Actions: ↑esophageal peristaltic amplitude, ↑lower esophageal sphincter pressure, ↑gastric emptying
    ▪ No effect on small intestine or colonic motility
    ▪ Other effects: block CTZ \( \rightarrow \) antinausea & antiemetic action
  o Domperidone: ↑hydrophilicity, ↓EPS, ↓bioavailability, not available in US

• Serotonin receptor antagonists
  o 5-HT3 receptors act in GI motility, secretion, and sensation (e.g. signaling of digestive reflexes, satiety, pain, discomfort from gut)
  o Gut distention \( \rightarrow \) enterochromaffin cells release 5-HT \( \rightarrow \) (+)IPANS \( \rightarrow \) (+)enteric neurons + release of ACh \( \rightarrow \) (+)peristaltic & secretory reflex activity

• 5-HT4 receptor agonists
  o Cisapride: partial 5-HT4 agonist without D2 antagonism (no EPS or CNS adverse effects); induces *torsades*
  o Prucalopride: symptomatic treatment of chronic constipation in women in whom laxatives fail; Europe only
  o Mosapride: treats chronic gastritis, GERD, functional dyspepsia; Japan only
  o Naronapride: metabolized by ubiquitous carboxylesterases to a single metabolites
  o Tegaserod: structurally related to 5-HT, partial 5-HT4 agonist; treats women with IBS constipation
Pumosetrag: locally acting 5-HT3 partial agonist; treats IBS constipation & nocturnal GERD; phase II trials

Chloride Channel Activators

- **Lubiprostone (Amitiza)**
  - (+) Specific chloride channel in GI tracts $\rightarrow$ ↑GI secretions $\rightarrow$ ↑H₂O + ↑Na $\rightarrow$ ↑GI transit
  - Indication: chronic idiopathic constipation, when all else fails
  - Pharmacokinetics: minimal systemic absorption, metabolized in lumen of GI tract

μ-Opioid Antagonists

- **Alvimopan (Entereg)**
  - Indication: post operative ileus under REMS
  - Zwitterionic form + polarity $\rightarrow$ limits GI absorption + prevents BBB passage $\rightarrow$ only peripherally acting

Laxatives

- Types of laxatives: bulk forming, osmotic, stool surfactants, and stimulants
- **Stimulant laxatives**
  - Anthraquinones: naturally occurring in plants (e.g. cascara, senna, aloe)
  - MOA: glycosides not absorbed by gut $\rightarrow$ transported to colon $\rightarrow$ bacteria act on it $\rightarrow$ hydrolyze glycoside bond $\rightarrow$ reduce anthraquinones to anthrones $\rightarrow$ (−)Na+K+ pump $\rightarrow$ ↑watery stool
  - Onset of action: delayed 6-8 hours after po dose
  - Potential for abuse: only use short term

IBD Drugs

- Current IBD treatments try to suppress inflammatory process
- Common drugs: mesalamine derivatives, corticosteroids, immunomodulators, biological response modifiers
- **Mesalamine derivatives (5-ASA):** rectal suspension enema has local effects, blocks COX, (−)prostaglandin synthesis in colon
- **Osalazine:** 5-ASA dimer linked by azo bond $\rightarrow$ converted to active ASA by bacteria in lower intestine
- **Sulfasalazine:** mesalamine + sulfapyridine $\rightarrow$ converted to active ASA by bacteria in lower intestine
- **Biologic therapy:** anti-TNFα agents (e.g. infliximab, etanercept)