טרופות הפועלות
במערכת העיכול

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DRUGS USED IN ACID-PEPTIC DISEASES
Acid-peptic diseases

- gastroesophagoeal reflux
- peptic ulcer (gastric and duodenal)
- stress-related mucosal injury

In these situations: Mucosal erosions or ulceration arise when the caustic effects of aggressive factors (acid, pepsin, bile) overwhelm the defensive factors of the gastrointestinal mucosa (mucus and bicarbonate secretion, prostaglandins, blood flow, and the processes of restitution and regeneration after cellular injury)
Over 90% of peptic ulcers are caused by:

- infection with the bacterium *Helicobacter pylori*
- use of nonsteroidal anti-inflammatory drugs (NSAIDs)
Drugs used in the treatment of acid-peptic disorders may be divided into two classes:

1. agents that reduce intragastric acidity

2. agents that promote mucosal defense
ANTACIDS

Used for:

- Dyspepsia
- Intermittent heartburn
Antacids are weak bases that react with gastric hydrochloric acid to form a salt and water.

Their principal mechanism of action is reduction of intragastric acidity.
Sodium bicarbonate

- eg, baking soda, Alka Seltzer

- reacts rapidly with hydrochloric acid (HCL) to produce carbon dioxide and sodium chloride

- Formation of carbon dioxide results in gastric distention and belching

- Unreacted alkali is readily absorbed, potentially causing metabolic alkalosis when given in high doses or to patients with renal insufficiency

- Sodium chloride absorption may exacerbate fluid retention in patients with heart failure, hypertension, and renal insufficiency
Calcium carbonate

- eg, Tums
- is less soluble and reacts more slowly than sodium bicarbonate with HCl to form carbon dioxide and calcium chloride (CaCl₂)
- Like sodium bicarbonate, calcium carbonate may cause belching or metabolic alkalosis
magnesium hydroxide or aluminum hydroxide

- eg, Maalox
- react slowly with HCl to form magnesium chloride or aluminum chloride and water

- Because no gas is generated, belching does not occur.

- Metabolic alkalosis is also uncommon because of the efficiency of the neutralization reaction

- Unabsorbed magnesium salts may cause an osmotic diarrhea
- Aluminum salts may cause constipation

- Patients with renal insufficiency should not take these agents long-term
All antacids may affect the absorption of other medications by:

- binding the drug (reducing its absorption)

- increasing intragastric pH so that the drug's dissolution or solubility (especially weakly basic or acidic drugs) is altered

Therefore, antacids should not be given within 2 hours of doses of tetracyclines, fluoroquinolones, itraconazole, and iron.
H2- antagonist

Four H₂ antagonists are in clinical use:
- cimetidine, ranitidine, famotidine, and nizatidine

- All four agents are rapidly absorbed from the intestine
- Cimetidine, ranitidine, and famotidine undergo first-pass hepatic metabolism resulting in a bioavailability of approximately 50%

- The serum half-lives of the four agents range from 1.1 to 4 hours; however, duration of action depends on the dose given
<table>
<thead>
<tr>
<th>Drug</th>
<th>Relative Potency</th>
<th>Dose to Achieve &gt; 50% Acid Inhibition for 10 Hours</th>
<th>Usual Dose for Acute Duodenal or Gastric Ulcer</th>
<th>Usual Dose for Gastroesophageal Reflux Disease</th>
<th>Usual Dose for Prevention of Stress-Related Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimetidine</td>
<td>1</td>
<td>400–800 mg</td>
<td>800 mg HS or 400 mg bid</td>
<td>800 mg bid</td>
<td>50 mg/h continuous infusion</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>4–10</td>
<td>150 mg</td>
<td>300 mg HS or 150 mg bid</td>
<td>150 mg bid</td>
<td>6.25 mg/h continuous infusion or 50 mg IV every 6–8 h</td>
</tr>
<tr>
<td>Nizatidine</td>
<td>4–10</td>
<td>150 mg</td>
<td>300 mg HS or 150 mg bid</td>
<td>150 mg bid</td>
<td>Not available</td>
</tr>
<tr>
<td>Famotidine</td>
<td>20–50</td>
<td>20 mg</td>
<td>40 mg HS or 20 mg bid</td>
<td>20 mg bid</td>
<td>20 mg IV every 12 h</td>
</tr>
</tbody>
</table>

BID, twice daily; HS, bedtime.
H₂ antagonists reduce acid secretion stimulated by histamine as well as by gastrin and cholinomimetic agents through two mechanisms:

- First, histamine released from ECL cells by gastrin or vagal stimulation is blocked from binding to the parietal cell H₂ receptor.

- Second, direct stimulation of the parietal cell by gastrin or acetylcholine has a diminished effect on acid secretion in the presence of H₂-receptor blockade.
- H₂ antagonists are especially effective at inhibiting nocturnal acid secretion (which depends largely on histamine)

- Recommended prescription doses maintain greater than 50% acid inhibition for 10 hours; hence, these drugs are commonly given twice daily

- At doses available in over-the-counter formulations, the duration of acid inhibition is less than 6 hours
GASTROESOPHAGEAL REFLUX DISEASE (GERD)

- Patients with infrequent heartburn or dyspepsia (fewer than 3 times per week) may take either antacids or intermittent H₂ antagonists

- Because antacids provide rapid acid neutralization, they afford faster symptom relief than H₂ antagonists

- H₂ antagonists may be taken prophylactically before meals in an effort to reduce the likelihood of heartburn

- Frequent heartburn is better treated with twice-daily H₂ antagonists or proton pump inhibitors

- In patients with erosive esophagitis (approximately 50% of patients with GERD), H₂ antagonists afford healing in less than 50% of patients; hence proton pump inhibitors are preferred because of their superior acid inhibition.
PREVENTION OF BLEEDING FROM STRESS-RELATED GASTRITIS

- Clinically important bleeding from upper gastrointestinal erosions or ulcers occurs in 1–5% of critically ill patients as a result of impaired mucosal defense mechanisms caused by poor perfusion.

- Although most critically ill patients have normal or decreased acid secretion, numerous studies have shown that agents that increase intragastric pH (H₂ antagonists or proton pump inhibitors) reduce the incidence of clinically significant bleeding.

- However, the optimal agent is uncertain at this time.

- For patients without a nasoenteric tube or with significant ileus, intravenous H₂ antagonists are preferable over intravenous proton pump inhibitors because of their proven efficacy and lower cost.

- Continuous infusions of H₂ antagonists are generally preferred to bolus infusions because they achieve more consistent, sustained elevation of intragastric pH.
**Table 62–2 Pharmacokinetics of Proton Pump Inhibitors.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>pKᵦ</th>
<th>Bioavailability (%)</th>
<th>$t_{1/2}$ (h)</th>
<th>$T_{max}$ (h)</th>
<th>Usual Dosage for Peptic Ulcer or GERD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>4</td>
<td>40–65</td>
<td>0.5–1.5</td>
<td>1–3.5</td>
<td>20–40 mg qd</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>4</td>
<td>&gt; 80</td>
<td>1.2–1.5</td>
<td>1.6</td>
<td>20–40 mg qd</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>4</td>
<td>&gt; 80</td>
<td>1.5</td>
<td>1.7</td>
<td>30 mg qd</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>3.9</td>
<td>77</td>
<td>1.0–1.9</td>
<td>2.5–4.0</td>
<td>40 mg qd</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>5</td>
<td>52</td>
<td>1.0–2.0</td>
<td>2.0–5.0</td>
<td>20 mg qd</td>
</tr>
</tbody>
</table>

GERD, gastroesophageal reflux disease.
Proton pump inhibitors are administered as inactive prodrugs

To protect the acid-labile prodrug from rapid destruction within the gastric lumen, oral products are formulated for delayed release as acid-resistant, enteric-coated capsules or tablets

After passing through the stomach into the alkaline intestinal lumen, the enteric coatings dissolve and the prodrug is absorbed

For children or patients with dysphagia or enteral feeding tubes, capsules may be opened and the microgranules mixed with apple or orange juice or mixed with soft foods (eg, applesauce).
H pylori-Associated Ulcers

The best treatment regimen consists of a 14-day regimen of "triple therapy":

- a proton pump inhibitor twice daily;
- clarithromycin, 500 mg twice daily;
- and either amoxicillin, 1 g twice daily, or metronidazole, 500 mg twice daily.

After completion of triple therapy, the proton pump inhibitor should be continued once daily for a total of 4–6 weeks to ensure complete ulcer healing.
**NSAID-Associated Ulcers**

- either $H_2$ antagonists or proton pump inhibitors provide rapid ulcer healing so long as the NSAID is discontinued;
- however continued use of the NSAID impairs ulcer healing.

- In patients with NSAID-induced ulcers who require continued NSAID therapy, treatment with a once- or twice-daily proton pump inhibitor more reliably promotes ulcer healing.
BISMUTH COMPOUNDS

- Bismuth coats ulcers and erosions, creating a protective layer against acid and pepsin.

- It may also stimulate prostaglandin, mucus, and bicarbonate secretion.

- Bismuth subsalicylate reduces stool frequency and liquidity in acute infectious diarrhea.

- Bismuth has direct antimicrobial effects and binds enterotoxins, accounting for its benefit in preventing and treating traveler's diarrhea.

- Bismuth compounds have direct antimicrobial activity against *H pylori*. 
Bismuth subsalicylate
(Kalbeten, pink-Bismuth, Pepto-Bismol)

- is used for the prevention of traveler's diarrhea (30 mL or 2 tablets four times daily).
Bismuth compounds are used in 4 drug regimen for the eradication of *H pylori* infection

- a proton pump inhibitor twice daily
- bismuth subsalicylate (2 tablets; 262 mg each)
- tetracycline (250–500 mg)
- metronidazole (500 mg) four times daily

for 10–14 days
DRUGS STIMULATING GASTROINTESTINAL MOTILITY
Drugs that can selectively stimulate gut motor function (prokinetic agents) have significant potential clinical usefulness.

- 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 the small intestine may be beneficial for postoperative ileus or chronic intestinal pseudo-obstruction

- Agents that enhance colonic transit may be useful in the treatment of constipation
CHOLINOMIMETIC AGENTS

- Cholinomimetic agonists such as bethanechol stimulate muscarinic M₃ receptors on muscle cells and at myenteric plexus synapses.

- Bethanechol was used in the past for the treatment of GERD and gastroparesis.

- Owing to multiple cholinergic effects and the advent of less toxic agents, it is now seldom used.
The acetylcholinesterase inhibitor neostigmine can enhance gastric, small intestine, and colonic emptying.

Intravenous neostigmine has enjoyed a resurgence in clinical usage for the treatment of hospitalized patients with acute large bowel distention.

Administration of 2 mg results in prompt colonic evacuation of flatus and feces in the majority of patients.

Cholinergic effects include excessive salivation, nausea, vomiting, diarrhea, and bradycardia.
METOCLOPRAMIDE & DOMPERIDONE

- They are dopamine D$_2$ receptor antagonists

- Within the gastrointestinal tract activation of dopamine receptors inhibits cholinergic smooth muscle stimulation; blockade of this effect is believed to be the primary prokinetic mechanism of action of these agents.

- These agents increase esophageal peristaltic amplitude, increase lower esophageal sphincter pressure, and enhance gastric emptying

- but have no effect on small intestine or colonic motility

- Metoclopramide and domperidone also block dopamine D$_2$ receptors in the chemoreceptor trigger zone of the medulla (area postrema), resulting in potent antinausea and antiemetic action
The most common adverse effects of metoclopramide involve the central nervous system:

- Restlessness, drowsiness, insomnia, anxiety, and agitation occur in 10–20% of patients, especially the elderly

- Extrapyramidal effects (dystonias, akathisia, parkinsonian features) due to central dopamine receptor blockade

- Elevated prolactin levels (caused by both metoclopramide and domperidone) can cause galactorrhea, gynecomastia, impotence, and menstrual disorders
Domperidone is extremely well tolerated

Because it does not cross the blood-brain barrier to a significant degree, neuropsychiatric and extrapyramidal effects are rare.
MACROLIDES

- Macrolide antibiotics such as erythromycin directly stimulate motilin receptors on gastrointestinal smooth muscle and promote the onset of a migrating motor complex.

- Intravenous erythromycin (3 mg/kg) 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.
BULK-FORMING LAXATIVES:

- Bulk-forming laxatives are indigestible, hydrophilic colloids that absorb water, forming a bulky, emollient gel that distends the colon and promotes peristalsis.

- Common preparations include natural plant products (psyllium, methylcellulose) and synthetic fibers (polycarbophil).

- Bacterial digestion of plant fibers within the colon may lead to increased bloating and flatus.
STOOL SURFACTANT AGENTS (SOFTENERS):

- These agents soften stool material, permitting water and lipids to penetrate.

- They may be administered orally or rectally.

- Common agents include docusate (oral or enema) and glycerin suppository.
Mineral oil

- is a clear, viscous oil that lubricates fecal material, retarding water absorption from the stool

- It is used to prevent and treat fecal impaction in young children and debilitated adults

- It is not palatable but may be mixed with juices

- Aspiration can result in a severe lipid pneumonitis

- Long-term use can impair absorption of fat-soluble vitamins (A, D, E, K).
OSMOTIC LAXATIVES

- The colon can neither concentrate nor dilute fecal fluid: fecal water is isotonic throughout the colon

- Osmotic laxatives are soluble but nonabsorbable compounds that result in increased stool liquidity due to an obligate increase in fecal fluid

- Magnesium hydroxide (milk of magnesia)
- Sorbitol
- Lactulose
Osmotic laxative

- The most commonly used purgatives are **magnesium citrate** and **sodium phosphate**

- High doses of osmotically active agents produce prompt bowel evacuation (purgation) within 1–3 hours

- The rapid movement of water into the distal small bowel and colon leads to a high volume of liquid stool followed by rapid relief of constipation.
Osmotic laxative

Balanced Polyethylene Glycol

- These balanced, isotonic solutions contain an inert, nonabsorbable, osmotically active sugar (PEG) with sodium sulfate, sodium chloride, sodium bicarbonate, and potassium chloride.

- The solution is designed so that no significant intravascular fluid or electrolyte shifts occur.

- Therefore, they are safe for all patients.

- The solution should be ingested rapidly (2–4 L over 2–4 hours) to promote bowel cleansing.
For treatment or prevention of chronic constipation, smaller doses of PEG powder may be mixed with water or juices (17 g/8 oz) and ingested daily.

In contrast to sorbitol or lactulose, PEG does not produce significant cramps or flatus.
STIMULANT LAXATIVES

- Direct stimulation of the enteric nervous system and colonic electrolyte and fluid secretion

- There has been concern that long-term use of cathartics could lead to dependence and destruction of the myenteric plexus, resulting in colonic atony and dilation

- More recent research suggests that long-term use of these agents probably is safe in most patients

- Cathartics may be required on a long-term basis, especially in patients who are neurologically impaired and in bed-bound patients in long-term care facilities.
Anthraquinone Derivatives

- **Aloe, senna, and cascara** (plants)

- Chronic use leads to a characteristic brown pigmentation of the colon known as "melanosis coli."

- There has been some concern that these agents may be carcinogenic, but epidemiologic studies do not suggest a relation to colorectal cancer.
Diphenylmethane Derivatives

- **Bisacodyl** is available in tablet and suppository formulations for the treatment of acute and chronic constipation.

- It also is used in conjunction with PEG solutions for colonic cleansing prior to colonoscopy.

- **Phenolphthalein**, another agent in this class, was removed from the market owing to concerns about possible cardiac toxicity.
ANTIDIARRHEAL AGENTS

OPIOID AGONISTS:

- Opioids have significant constipating effects

- They increase colonic phasic segmenting activity through inhibition of presynaptic cholinergic nerves in the submucosal and myenteric plexuses and lead to increased colonic transit time and fecal water absorption

- They also decrease mass colonic movements and the gastrocolic reflex

- Although all opioids have antidiarrheal effects, central nervous system effects and potential for addiction limit the usefulness of most
Loperamide:

- Is a nonprescription opioid agonist
- Does not cross the blood-brain barrier
- Has no analgesic properties or potential for addiction
- Tolerance to long-term use has not been reported
- It is typically administered in doses of 2 mg taken one to four times daily
5-HT₃ antagonists

- are a class of medications that act as receptor antagonists at the 5-HT₃ receptor, a subtype of serotonin receptor found in terminals of the vagus nerve and in certain areas of the brain.

- Almost all 5-HT₃ antagonists are antiemetics, used in the prevention and treatment of nausea and vomiting.

- They are particularly effective in controlling the nausea and vomiting produced by cancer chemotherapy and are considered the gold standard for this purpose.
Comparative pharmacology of 5-HT3 receptor antagonist[10]

<table>
<thead>
<tr>
<th>Drug</th>
<th>Chemical nature</th>
<th>Receptor antagonists</th>
<th>T$_{1/2}$ (h)</th>
<th>Metabolism</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ondansetron</td>
<td>Carbazole derivative</td>
<td>5-HT$_3$ receptor antagonist and weak 5-HT$_4$ antagonist</td>
<td>3.9 hours</td>
<td>CYP1A1/2, CYP2D6, CYP 3A3/4/5</td>
<td>0.15 mg/kg</td>
</tr>
<tr>
<td>Granisetron</td>
<td>Indazole</td>
<td>5-HT$_3$ receptor antagonist</td>
<td>9-11.6 hours</td>
<td>CYP3A3/4/5</td>
<td>10 µg/kg</td>
</tr>
</tbody>
</table>
CORTICOSTEROIDS

- Corticosteroids (dexamethasone, methylprednisolone) have antiemetic properties, but the basis for these effects is unknown.

- These agents appear to enhance the efficacy of 5-HT$_3$-receptor antagonists for prevention of acute and delayed nausea and vomiting in patients receiving moderately to highly emetogenic chemotherapy regimens.

- Although a number of corticosteroids have been used, dexamethasone, 8–20 mg intravenously before chemotherapy, followed by 8 mg/d orally for 2–4 days, is commonly administered.
NEUROKININ RECEPTOR ANTAGONISTS

- Neurokinin 1 (NK₁)-receptor antagonists have antiemetic properties that are mediated through central blockade in the area postrema.

- **Aprepitant** (an oral formulation) is a highly selective NK₁-receptor antagonist that crosses the blood-brain barrier and occupies brain NK₁ receptors.

- It has no affinity for serotonin, dopamine, or corticosteroid receptors.

- **Fosaprepitant** is an intravenous formulation that is converted within 30 minutes after infusion to aprepitant.
PHENOTHIAZINES & BUTyroPHENONES

- Phenothiazines are antipsychotic agents that can be used for their potent antiemetic and sedative properties.

- The antiemetic properties of phenothiazines are mediated through inhibition of dopamine and muscarinic receptors.

- Sedative properties are due to their antihistamine activity.

- The agents most commonly used as antiemetics are prochlorperazine, promethazine, and thiethylperazine.
Antipsychotic butyrophenones also possess antiemetic properties due to their central dopaminergic blockade.

The main agent used is droperidol, which can be given by intramuscular or intravenous injection.

In antiemetic doses, droperidol is extremely sedating.
H₁ ANTIHISTAMINES & ANTICHOLINERGIC DRUGS

- As single agents, these drugs have weak antiemetic activity, although they are particularly useful for the prevention or treatment of motion sickness.

- Their use may be limited by dizziness, sedation, confusion, dry mouth, cycloplegia, and urinary retention.

- Diphenhydramine and one of its salts, dimenhydrinate, are first-generation histamine H₁ antagonists that also have significant anticholinergic properties.

- Because of its sedating properties, diphenhydramine is commonly used in conjunction with other antiemetics for treatment of emesis due to chemotherapy.