Treatment of Gastrointestinal Disorders

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Drugs Used Primarily for Gastrointestinal Conditions

- Drugs used in acid-peptic diseases
- Drugs stimulating motility
- Laxatives
- Antidiarrheal drugs
- Drugs for irritable bowel syndrome
- Antiemetic Drugs
- Drugs used in inflammatory bowel disease
- Pancreatic supplements
- Bile acid therapy for gallstones
- Drugs used to treat variceal hemorrhage
Acid-Peptic Diseases

• Dyspepsia
• Peptic ulcer disease (PUD)
• Gastroesophageal reflux disease (GORD/GERD)
• Extraesophageal reflux disease
• Barrett's esophagus
• Prevention of stress gastritis
• Gastrinomas and other conditions that cause hypersecretion of acid
• Zollinger-Ellison syndrome
Dyspepsia

• Chronic or recurrent pain in the upper abdomen
• Upper abdominal fullness
• Feeling full earlier than expected when eating
• Bloating
• Belching
• Nausea
• Heartburn

• Frequently due to gastroesophageal reflux disease (GERD) or gastritis, but in a small minority may be the first symptom of peptic ulcer disease (an ulcer of the stomach or duodenum) and occasionally cancer. Hence, unexplained newly-onset dyspepsia in people over 55 or the presence of other alarm symptoms may require further investigations
Gastritis

• The most common symptom is abdominal upset or pain
• Other symptoms are indigestion, abdominal bloating, nausea, and vomiting
• Some may have a feeling of fullness or burning in the upper abdomen
• Gastroscopy, blood tests, complete blood counts and/or a stool guaiac test may be used to diagnose gastritis
• Treatment includes taking antacids or other medicines, such as proton pump inhibitors or antibiotics, or avoiding hot or spicy foods
• For those with pernicious anemia, B_{12} injections are given
Gastrinomas

A gastrinoma is a tumor that secretes gastrin.
Extraesophageal reflux disease

retrograde flow of gastric contents to the upper aerodigestive tract

Symptoms:

cough
hoarseness
asthma
others.
Barrett's esophagus

• normal lining of the esophagus (squamous epithelium) is replaced by an intestinal-type lining (columnar epithelium).

• caused by damage from chronic acid exposure, or reflux esophagitis

• found in 5-15% of patients who seek medical care for heartburn (gastroesophageal reflux disease, GERD)

• large subgroup of patients with Barrett's esophagus do not have symptoms

• a premalignant condition associated with an increased risk of esophageal cancer
Zollinger-Ellison syndrome

• A disorder where increased levels of the hormone gastrin are produced, causing the stomach to produce excess hydrochloric acid

• Often the cause is a tumor (gastrinoma) of the duodenum or pancreas producing the hormone gastrin

• Gastrin then causes an excessive production of acid which can lead to peptic ulcers in up to 95% of patients
Regulation of Gastric Acid Secretion
Anatomy of the stomach

- Fundus
- Esophagus
- Antrum
- Pylorus
- Duodenum
Fundus

Antrum

Body

Pylorus

Duodenum

Antrum

Gastric pit

Esophagus

Mucous cells

Parietal cells

ECL cells

Chief cells

D cells

G cells

Anatomy of the stomach II
Mucous cells

Gastric pits

Parietal cells

Enterochromaffin-like cells

Chief cells

D cells

G cells

Mucous, bicarbonate

Gastric acid, Intrinsic factor

Histamine, serotonin

Pepsin(ogen), Gastric lipase

Somatostatin (inhibits acid)

Gastrin (stimulates acid)
Parietal cell function
Gastrin and somatostatin
Parietal cell function

- Vagus preganglionic nerve
- Fundic blood vessel
- Gastrin
- ECL cell
- Histamine
- $M_3$-R
- Ach
- $H_2$-R
- $G/{\text{CCk}}$-R
- Parietal cell
- $H^{+}/K^{+}$ ATPase
- Luminal acid

Lumen of fundus
Antacids

Weak bases
Form a salt and water
Reduce intragastric acidity
Antacids

• Sodium bicarbonate (baking soda, Alka Seltzer)
• Calcium carbonate (Tums, Os-Cal)
• Magnesium hydroxide (diarrhea)
  Aluminum hydroxide (constipation)
• Magnesium and aluminum hydroxide together
  (Celusil, Maalox, Mylanta)
Antacids

• Belching
• Metabolic alkalosis
• Fluid retention (patients with heart failure)
• Hypercalcemia with calcium carbonate
• Magnesium and aluminum hydroxide excreted by the kidneys, not to be taken by patients in renal failure.
H$_2$-Receptor Antagonists

- Cimetidine (Tagamet®)
- Ranitidine (Zantac®)
- Nizatidine (Axd®)
- Famotidine (Pepcid®)
H₂-Receptor Antagonists

• Reduce basal and meal-induced acid secretion
• Decrease histamine, gastrin and ACh-stimulated acid secretion
• Significant “first-pass” effect for all but nizatidine
• Especially effective with nocturnal acid secretion
• Gradually being replaced by proton pump inhibitors
H$_2$-Receptor Antagonists

• Gastroesophageal reflux disease (GERD)
• Peptic ulcer disease (H. pylori)
• Non-ulcer dyspepsia
• Present bleeding from stress-related gastritis
H$_2$-Receptor Antagonists

• Extremely safe drugs
• Fewer than 3% of patients experience diarrhea, headache, fatigue, myalgias, and constipation
• Changes in mental status (confusion, hallucinations, agitation)
• Gynecomastia or impotence in men
• Galactorrhea in women
• Cross placenta in pregnant women
• Rare blood dyscrasias
• Drug interactions (especially cimetidine)
Proton Pump Inhibitors

• Omeprazole (Prilosec®)
• Esomeprazole (Nexium®)
• Lansoprazole (Prevasid®)
• Pantoprazole (Protonix®)
• Rabeprazole (Aciphex®)
Proton Pump Inhibitors

• Are administered as inactive pro-drugs

• Active form is a reactive thiophilic sulfenamide cation, which forms a covalent disulfide bond with the $\text{H}^+, \text{K}^+$ ATPase, irreversibly inactivating the enzyme

• Inhibit both fasting and meal-stimulated secretion

• Rapid “first-pass” and systemic hepatic metabolism

• Short serum half-life, concentrated and activated near site of action, have a long duration of action
Therapeutic Uses of Proton Pump Inhibitors

• Gastroesophageal reflux disease (GERD)
• Peptic ulcer disease (used with antibiotics designed to kill H pylori)
• NASID-induced ulcers
• Prevention of re-bleeding of peptic ulcers
• Non-ulcer dyspepsia (value not established)
• Prevention of stress-related mucosal bleeding (i.v. H$_2$-receptor antagonists are preferred)
• Gastrinomas and other hypersecretory conditions
Adverse Effects of Proton Pump Inhibitors

• Extremely safe
• Decreased $B_{12}$ levels
• Respiratory and enteric infections
• Potential danger of increased circulating gastrin levels
• Potential of increased inflammation of stomach
Acid (control)

H₂ block

PPI

Gastric acid secretion – by time of day
Mucosal Protective Agents

• Sucralfate
• Prostaglandin analogs
• Bismuth compounds
Sulcralfate (Carafate®)

• Salt of sucrose complexed to sulfated aluminum hydroxide
• Forms a viscous, tenacious paste that binds selectively to ulcers and erosions
• Mechanism unknown
• Given 4x daily orally on an empty stomach
• Virtually free of adverse effects
• Might bind to other drugs which are taken orally
Mesoprostol (Cytotec®)

• Stimulates mucus and bicarbonate secretion and enhance mucosal blood flow
• Blocks prostaglandin receptors on parietal cells to reduce acid production
• Used to treat patients who receive long-term NSAID’s
• Diarrhea and cramping abdominal pain in 10-20% of patients
Bismuth Compounds

• Bismuth subsalicylate (found in Kaopectate® and Pepto-Bismol®) and bismuth subcitrate potassium (Pylera®)
• Coats ulcers and erosions creating a protective layer against acid and pepsin
• Might stimulate prostaglandin, mucus and bicarbonate secretion
• Reduces stool frequency and liquidity in acute, infectious diarrhea
• Direct antimicrobial activity against H. pylori
Conditions Leading to Nausea and Vomiting

- Use of medications
- Systemic disorders and infections
- Pregnancy
- Vestibular dysfunction
- CNS infection
- Increased intracranial pressure
- Peritonitis
- Hepatobiliary disorders
- Radiation and cancer chemotherapy
- GI obstruction, dysmotility or infection
Neural pathways for nausea and vomiting

Sensory neurons in stomach

Vestibular system
- H₁ receptor?
- M₁ receptor

Chemoreceptor trigger zone (area postrema)
- Chemoreceptors
- D₂ receptor
- NK₁ receptor?
- (S-HT₅ receptor)

Vomiting center (nucleus of tractus solitarius)
- H₁ receptor
- M₁ receptor
- NK₁ receptor?
- (S-HT₅ receptor)

Central nervous system
- Cortex
- Thalamus
- Hypothalamus
- Meninges

Gastrointestinal tract and heart
- Mechanoreceptors
- Chemoreceptors
- S-HT₅ receptor

Fourth ventricle
- Medulla oblongata
- Cranial nerve IX or X
- Parasympathetic and motor efferent activity
Classes of Drugs used to Nausea and Vomiting

• Serotonin 5-HT<sub>3</sub> Antagonists
• Corticosteroids
• Neurokinin Receptor Antagonists
• Phenothiazines and Butyrophenones
• Substituted Benzamides
• H<sub>1</sub> Antihistamines and Anticholinergic Drugs
• Benzodiazepines
• Cannabinoids
Serotonin 5-HT$_3$ Antagonists

• Odansetron (Zofran®)
• Granisetron Granisol®
• Dolasetron (Anzemet)
• Palonosetron (Aloxi®)
• Tropisetron (Navoban®)
Serotonin 5-HT\textsubscript{3} Antagonists

• Odansetron, granisetron and dolasetron have a t\textsubscript{1/2} of 4 to 9 hours
• Can be given orally or i.v.
• Palonosetron has a t\textsubscript{1/2} of 40 hours and is given i.v.
• Tropisetron is available outside of the United States
• None block dopamine or muscarinic receptors
• Have no effect on esophageal or gastric motility but might slow colonic transit
Serotonin 5-HT$_3$ Antagonists

Clinical Uses

- Chemotherapy-induced nausea and vomiting
- Postoperative and post radiation nausea and vomiting
Serotonin 5-HT$_3$ Antagonists

Adverse Effects

- Extremely safe and well-tolerated
- Most common adverse effects are headache, dizziness and constipation
- Prolongation of the QT interval, mainly with dolasetron

Drug Interactions

Metabolized by CYP450’s but no significant drug interactions
Corticosteroids

• Dexamethasone
• Methylprednisolone

Used to treat acute and delayed nausea in patients receiving moderately to highly emetogenic chemotherapy regimens.
Neurokinin Receptor Antagonists

• Aprepitant (Emend®)
• Phosaprepitant

Used in combination with 5-HT3 receptor antagonists and corticosteroids for acute and delayed nausea and vomiting from highly emetogenic cancer chemotherapeutic regimens. Metabolized by CYP3A4
Phenothiazines and Butyrophenones

- Prochlorperazine (Compazine®)
- Promethazine (Phenergan®)
- Thiethylperazine (Torecan®)

- Droperidol (Inapsine®)
Phenothiazines and Butyrophenones

- Prochlorperazine (Compazine®)
- Promethazine (Phenergan®)
- Thiethylperazine (Torecan®)
- Droperidol (Inapsine®)
H₁-Receptor Antagonists and Muscarinic Antagonists

• Diphenhydramine (Benadryl®)
• Dimenhydrinate (Dramamine®)
• Meclizine (Antivert®)
• Scopolamine (Hyoscine)
Classes of Drugs used to Nausea and Vomiting

• Substituted Benzamides
• Benzodiazepines
• Cannabinoids