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Pharmacology of Common Agents Used in Gastrointestinal Conditions

Common agents used in GERD/Hyperacidity

Proton Pump Inhibitors (PPI)

- They are pro-drugs that require activation in an acidic environment. They get activated in gastric parietal cells and inhibit the H^+/K^+ ATPase enzyme system (proton pump), thereby inhibiting acid secretion
- Adverse effects
    - Generally well tolerated
    - Possible rebound increase in gastric acidity upon discontinuation of medication
    - Associated with an increased risk for developing acute gastroenteritis and community acquired pneumonia
- Examples of drugs in this class
    - Lansoprazole (safety/efficacy in children under 1 years of age has not been studied)
    - Omeprazole (FDA approved for children over 1 years of age)
    - Pantoprazole (limited data for use in children)
    - Rabeprazole (safety/efficacy in children under 18 years of age has not been studied)

H2 receptor antagonists

- They reduce acid secretion by acting as competitive, reversible inhibitors of the H_2 receptor. They also decrease the acid-secretory response of the parietal cell to stimulated acid secretion from cholinergic agents, gastrin, food and vagal stimulation
- Tolerance to acid suppressing effects of H_2 blockers is common with continued drug administration (can be as early as 3 days into course of treatment). This is not seen with the PPIs
- Adverse effects
    - Abdominal pain, bradyarrhythmia (rare)
    - Possible rebound increase in gastric acidity upon discontinuation of medication
    - Associated with an increased risk for developing acute gastroenteritis and community acquired pneumonia
- Examples of drugs in this class
    - Ranitidine
    - Famotidine
- Dosing
    - Dose adjustments need to be made for patient with renal impairment

Common Agents Used for Bowel Motility

Dopamine receptor antagonists

- Dopamine reduces lower esophageal sphincter and intragastric pressures. This is mediated by suppression of acetylcholine (Ach) release from myenteric motor neurons
- By antagonizing the inhibitory effect of dopamine of myenteric motor neurons, dopamine receptor antagonists are effective as prokinetic agents. They also help relieve nausea and vomiting by antagonizing dopamine receptors in the chemoreceptor trigger zone
- Direct activation of muscarinic receptors is not a very effective strategy for treating GI motility disorder because they enhance contractions in an un-coordinated fashion. This produces little propulsive activity
- Dopamine receptor antagonists don't have significant effects on lower GI motility (eg: small bowel dysmotility)
- Adverse effects
    - Extrapyrimidal symptoms (EPS), headache, fatigue, asthenia, neuroleptic malignant syndrome (rare)
- Examples of drugs in this class
    - Metoclopramide (useful in gastroparesis, as it accelerates gastric emptying and also has antiemetic effects)
        - Dose adjustments needed for patients with renal impairment
    - Domperidone
        - Predominantly antagonizes D_2 receptors. It is less likely to cause EPS, as it doesn't readily cross the blood-brain barrier
        - Use in children is not recommended unless in chemotherapy or radiation-induced nausea/vomiting

Common Agents Used for Constipation

Osmotically active agents

- They produce an osmotic effect in the colon to cause water retention, distension and promotion of peristalsis
- Adverse effects
    - Abdominal distension and discomfort, flatulence
- Examples of drugs in this class
    - Saline laxatives such as magnesium citrate (need to be used with caution in patients with renal insufficiency)
    - Nondigestible sugars and alcohols (eg: lactulose)

Stool softeners and emollients

- Reduces surface tension of the oil—water interface of the stool. This leads to enhanced incorporation of water and fat into the stools to soften them
- Patients taking these medications need to have adequate fluid intake
- Examples of drugs in this class
    - Docusate salts

        - Contraindicated in concomitant use of mineral oil, intestinal obstruction, acute abdominal pain, nausea, vomiting
    - Mineral oil
        - Rare lipid pneumonitis due to aspiration can occur, so 'heavy' mineral oil should not be taken at bed time, and 'light (topical)' mineral oil should never be administered orally
        - Contraindicated in patients with a colostomy, ileostomy, appendicitis, ulcerative colitis, diverticulitis, dysphagia, or hiatal hernia

Stimulants

- They have direct effects on enterocytes, enteric neurons and GI smooth muscle. They likely induce low-grade inflammation in the small and large bowel to promote accumulation of water an electrolytes and stimulate intestinal motility
- Prolonged use of these medications should be avoided, as it can lead to dependence
- Contraindicated in patients with undiagnosed abdominal pain, appendicitis, intestinal obstruction or perforation
- Examples of drugs in this class
    - Senna, castor oil, bisacodyl

Enemas and Suppositories

- Enemas cause direct bowel distension, and produces an evacuation reflex in most people. Some enemas have additional substances that are either osmotically active or irritant
- Glycerin acts a hydroscopic agent and lubricant when given rectally. The resultant water retention stimulates peristalsis and usually produces a bowel movement in less than 1 hour. Glycerin is for rectal use only, as the oral form is absorbed, and doesn't reach the bowel to exert this effect

Common Anti-diarrheal agents

Bismuth subsalicylate (Pepto-Bismol)

- It adsorbs extra water in large intestine, as well as toxins. It forms a protective coat on the intestinal mucosa, and appears to have antisecretory and antimicrobial effects
- It is contraindicated in children or teenagers with or recovering from influenza or varicella (risk of Reye's syndrome). It is also contraindicated in patients with a history of severe GI bleeding or coagulopathy
- Use caution in children < 3 years of age
- Adverse effect:
    - dark stools (sometimes mistaken for melena), impaction may occur in infants and debilitated patients

Opioids

- They act by several different mechanisms, mediated mainly though either u or delta opioid receptors on enteric nerves, epithelial cells, and muscle. Together, they inhibit intestinal motility (μ receptors), intestinal secretion (δ receptors), or absorption (μ and δ receptors)
- Opioids that do not penetrate the CNS are preferred over ones that do
- Adverse effects
    - Drowsiness (unlikely), risk of toxic megacolon, xerostomia, urinary retention
- Examples of drugs in this class

    - Loperamide (acts mainly via peripheral μ opioid receptors)
        - Increases small intestinal and mouth to cecum transit time, and increases anal sphincter tone
        - Use caution in patients with active inflammatory bowel disease involving the colon because of the risk for toxic megacolon
        - Contraindicated in children < 24 months of age; ulcerative colitis; infectious diarrhea that results from organisms that penetrate the intestinal mucosa; bloody diarrhea

Antinausseants and antiemetic agents

- Vomiting is controlled by the vomiting center of the medulla, and has input from at least 4 sources (chemoreceptor trigger zone, cortex, vestibular apparatus, GI tract). These pathways mediated by neurotransmitters (eg: 5HT)
- Since multiple neurotransmitters are involved in vomiting, a number of agents from various drug classes can be used to treat vomiting
- Various clinical factors (eg: emetogenic potential of chemo drugs) determine efficacy of antiemetics

Dopamine receptor antagonists

- Promethazine
    - Blocks postsynaptic mesolimbic dopaminergic receptors in the brain
    - Caution: avoid use in children <2years of age due to potential fatal respiratory depression. Also avoid use with any medications that may have respiratory depressant effects
    - Adverse effects: risk of neuroleptic malignant syndrome (esp. when used with antipsychotic drugs), phototoxicity, xerostomia, CNS depression, lowered convulsive threshold, respiratory depression
- Phenothiazines (eg: prochlorperazine, chlorpromazine)
    - They are D_2 receptor antagonists at the CTZ. They are not as effective in cancer or chemo induced emesis as ondansetron or metoclopramide
    - They also have antihistamine and anticholinergic properties which are useful in other forms of nausea such as motion sickness
- Metoclopramide
    - Dose adjustment needed for patients with renal impairment
- Adverse effects: drowsiness, EPS, hallucination, convulsion, neuroleptic malignant syndrome (rare), photosensitivity

Antihistamine

- Dimenhydrinate
    - Competes with histamine for H_1 receptor sites on effector cells in the GI tract, blood vessels, and respiratory tract. This diminishes vestibular stimulation and depresses labyrinthine function through central anticholinergic activity
    - Caution in neonates (gasping syndrome: metabolic acidosis, respiratory distress, gasping respirations, CNS dysfunction, hypotension, cardiovascular collapse) because of benzyl alcohol in the IV formulation
    - Approved for children ≥2 years of age
    - Use of the IV route in children is not recommended (use IM instead)

- Adverse effects: drowsiness, xerostomia, blurred vision (rare)

Glucocorticoids and anti-inflammatory agents

- They can be useful in patient with widespread cancer, possibly by suppressing peritumoral inflammation and prostaglandin production

Serotonin antagonist

- They inhibit $5HT_3$ receptors present both centrally (medullary chemoreceptor zone) and peripherally (GI tract) to inhibit visceral afferent stimulation of the vomiting center
- Examples of drugs in this class:
    - Ondansetron
        - Effective in preventing chemo or radiation induced nausea and vomiting, with very few adverse effects
        - Oral ondansetron therapy, as a single dose, can be used for infants and children who present to the emergency department with vomiting related to suspected acute gastroenteritis, and who have mild to moderate dehydration
        - There is no FDA approved dose for children < 4 years of age, but dosing based on body surface area has been used
        - Adverse effects:
            - Most common is diarrhea (thus it is not recommended in patients who are complaining of diarrhea), anxiety, drowsiness, headache
            - Potential to block cardiac sodium or potassium channels, resulting in prolongation of QRS/QTc interval respectively
    - Granisetron, dolasetron, palonosetron

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