Drugs Used in Gastrointestinal Diseases -2

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Drugs Used to Control Nausea and Vomiting

Two brainstem sites have key roles in the vomiting reflex pathway.

1. Chemoreceptor trigger zone (in area postrema at the caudal end of fourth ventricle) is outside the blood-brain barrier.
2. Vomiting center (in the lateral reticular formation of the medulla, coordinates the motor mechanisms of vomiting).

- The vomiting center also responds to afferent input from the vestibular system, the periphery (pharynx and gastrointestinal tract), and higher brainstem and cortical structures.
- The vestibular system functions mainly in motion sickness.

Causes of Nausea and Vomiting

- Motion sickness
- Pregnancy
- Hepatitis
- Chemotherapeutic agents

Classes of Anti Emetic

- Phenothiazines
- Serotonin-receptor blockers
- Benzamides
- Butyrophenones
- Benzodiazepines
- Corticosteroids
- Cannabinoids
- Substance P/neurokinin-1-receptor blocker

Phenothiazines

Prochlorperazine

Thiethylperazine

- Blocking dopamine receptors
- They are effective against low or moderately emetogenic chemotherapeutic agents

Side Effects

1. Hypotension and restlessness (dose-limiting).
2. Extrapyramidal symptoms and sedation.

Serotonin-Receptor Blockers (5-HT3 Receptor Blockers)

Ondansetron

Granisetron

Palonosetron

Dolasetron

Mechanism of Action of 5-HT3 Receptor Blockers

- Selectively block 5-HT3 receptors
- In the periphery (visceral vagal afferent fibers)
- In the brain (chemoreceptor trigger zone).

Pharmacokinetic of 5-HT3 Receptor Blockers

- These drugs can be administered as a single dose prior to chemotherapy (intravenously or orally)
- Long duration of action.
- Metabolized by the Liver to an active metabolite, eliminated through the urine.

Side Effect of 5-HT3 Receptor Blockers

1. Headache (common side effect).
2. Prolongation of QT Interval (with dolasetron)

Benzamides

Metoclopramide is highly effective at high doses against cisplatin, preventing emesis in 30-40%

Side Effects

Antidopaminergic side effects (sedation, diarrhea and extrapyramidal symptoms)

Butyrophenones
Droperidol
Domperidone
Haloperidol

- Act by blocking dopamine receptors.
- Moderately effective antiemetics.
- Droperidol had been used for sedation in endoscopy and surgery (in combination with opiates or benzodiazepines).
- Haloperidol or metoclopramide uesd for preventing cisplatin-induced emesis.
- The most important side effects is prolong the QT interval

Benzodiazepines

Lorazepam

Alprazolam

- Used in treating anticipatory vomiting.
- Beneficial effects due to their sedative, anxiolytic and amnesic properties.

Corticosteroids

Dexamethasone

Methylprednisolone

- Their antiemetic mechanism may involve blockade of prostaglandins.
- Effective against mildly to moderately emetogenic chemotherapy.
- Used alone or in combination with other agents.

Cannabinoids
Marijuana Derivatives (Dronabinol & Nabilone)

- Effective against moderately emetogenic chemotherapy.

Side Effects

- Dysphoria, hallucinations, sedation, vertigo and disorientation.

Substance P/Neurokinin-1-Receptor Blocker Aprepitant

- Antagonist to neurokinin receptor in the brain.
- Administered orally with dexamethasone and palonosetron
- little or no affinity for serotonin (5-HT3), dopamine, and corticosteroid receptors
- Used for chemotherapy-induced nausea & vomiting and postoperative nausea and vomiting
- Metabolisd by CYP3A4.
- Can also induce this enzyme

Side Effects

- Constipation and fatigue (the major side effects).

Combination Regimens

Combination of Antiemetic Drugs

- Increase antiemetic activity
- Decrease toxicity.
- Dexamethasone + metoclopramide, a 5-HT 3 antagonist, phenothiazine, butyrophenone, a cannabinoid, or a benzodiazepine
- Antihistamines (diphenhydramine + metoclopramide or corticosteroids)
- Supplementing a cannabinoid + prochlorperazine diminishes dysphoria

Antidiarrheals

1. Antimotility agents
2. Adsorbents
3. Agents that modify fluid and electrolyte transport

Antimotility agents

Diphenoxylate

Loperamide

- Analogues of meperidine
- Have opioid-like actions on the gut, activating presynaptic opioid receptors in the enteric nervous system (inhibit Ach release and decrease peristalsis).

Side Effects

- Drowsiness, abdominal cramps and dizziness.
- Toxic megacolon (they should not be used in young children or in patients with severe colitis).

Mechanism of Action

- Loperamide acts directly on circular and longitudinal intestinal muscles, through the opioid receptor
- Inhibits peristalsis and prolong transit time
- Reduces fecal volume
- Increases viscosity
- Diminishes fluid and electrolyte loss
- Has antisecretory activity
- Increases tone on anal sphincter

Adsorbent Agents

Kaolin

Pectin

Methylcellulose.

less effective than antimotility agents, causing constipation and interfere with absorption of other drugs.

Agents that Modify Fluid and Electrolyte Transport

NSAIDs (aspirin and indomethacin)

- Effective in controlling diarrhea (due to inhibition of prostaglandin synthesis).

Bismuth Subsalicylate

- Salicylate component, inhibits intestinal PG & Cl secretion (decreases fluid secretion in the bowel), used for traveler's diarrhea
- Has antimicrobial effects and binds enterotoxins
- Has activity against H pylori

Side Effect of Bismuth Subsalicylate

1. Stool blackening
2. Darkening of tongue
3. Encephalopathy (ataxia, headaches, confusion, seizures)

Laxatives

- Accelerate the movement of food through GIT.

Classification According to Mechanism of Action

1. Irritants and stimulants of the gut
2. Bulking agents
3. Stool softeners

Irritants and Stimulants

Castor Oil

- Castor oil is broken down in the small intestine to very irritating acid to the gut
- Increases peristalsis
- Stimulate uterine contractions (avoided in pregnant woman)

Cascara, Senna and Aloe

- Stimulate colonic activity
- Taken orally
- Causes evacuation of the bowels within 8 to 10 hours
- It also causes water and electrolyte secretion into the bowel.

Bisacodyl

- Potent stimulant of the colon. It acts directly on nerve fibers in the mucosa of the colon
- Available as suppositories and enteric-coated tablets
- Cause abdominal cramps and potential for atonic colon with prolonged use.

Bulk Laxatives

Hydrophilic Colloids

- From indigestible parts of fruits and vegetables
- Form gels in the large intestine
- Causing water retention and intestinal distension and increasing peristaltic activity.

Methylcellulose

Psyllium Seeds

Bran

- Have similar actions
- May cause intestinal obstruction.

Saline and osmotic laxatives

Saline cathartics (magnesium citrate, magnesium sulfate, sodium phosphate, and magnesium hydroxide)

- Nonabsorbable salts, hold water in the intestine by osmosis and distend the bowel, increasing intestinal activity and producing defecation in a few hours.

Lactulose

- Semisynthetic disaccharide sugar ,acts as an osmotic laxative (not hydrolyzed by intestinal enzymes).
- Oral doses are degraded in the colon by colonic bacteria into lactic, formic and acetic acids. This increases osmotic pressure, thereby accumulating fluid, distending the colon, creating a soft stool, and causing defecation.

Stool softeners (emollient laxatives or surfactants)

Docusate sodium

Docusate calcium

Docusate potassium

- Surface-active agents (become emulsified with the stool produce softer feces
- Take days to become effective.

Lubricant laxatives

- Mineral oil and glycerin suppositories are considered to be lubricants(facilitate the passage of hard stools)
- Mineral oil should be taken orally in an upright position (to avoid its aspiration and lipid or lipoid pneumonia).

Drugs Used in Inflammatory Bowel Disease (IBD)

Antidiarrheals

loperamide

- Helpful in reducing stool frequency

Fiber Supplements

- For patients with predominant constipation

Antispasmodics (Anticholinergics)

Dicyclomine

Hyoscyamine

- Relief of abdominal pain or discomfort through antispasmodic actions..
- At higher doses they exhibit significant additional anticholinergic effects (dry mouth, visual disturbances, urinary retention and constipation).

Serotonin 5-HT_3-Receptor Antagonists

Alosetron

- It is a 5-HT_3 antagonist that has been approved for the treatment of patients with severe irritable bowel syndrome with diarrhea
- Efficacy of the other 5-HT_3 (ondansetron, granisetron, dolasetron&palonosetron in the treatment of irritable bowel syndrome has not been determined.

Aminosalicylates Containing 5-aminosalicylic Acid

Mechanism of Action of 5-ASA

- Inhibiting the synthesis of prostaglandins and inflammatory leukotrienes and interfering with the production of inflammatory cytokines.
- Mesalamine, is absorbed from the small intestine whereas absorption from the colon is extremely low.

Balsalazide, Olsalazine and Sulfasalazine

- The azo structure is poorly absorbed in the small intestine.

Sulfasalazine (a Combination of 5-ASA and Sulfapyridine)

- Has a higher incidence of adverse effects that the other 5-ASA drugs, due to the systemic absorption of the sulfapyridine moiety.

Side Effect of Sulfasalazine

- Nausea, gastrointestinal upset, headaches, arthralgias, myalgias, bone marrow suppression, malaise and severe hypersensitivity reactions.

Glucocorticoids

- Inhibit production of inflammatory cytokines (TNF-α, IL-1) and chemokines (IL-8); reduce expression of inflammatory cell adhesion molecules and inhibit gene transcription of nitric oxide synthase, phospholipase A_2, cyclooxygenase-2 and NF-Kb

Prednisone and Prednisolone

- Most commonly used oral glucocorticoids in GIT
- Have an intermediate duration of biologic activity allowing once-daily dosing.
- Hydrocortisone enemas, foam, or suppositories are used to maximize colonic tissue effects and minimize systemic absorption.

Purine analoge

Azathioprine and 6-MP

- Purine antimetabolites
- Important agents in the induction and maintenance of remission of ulcerative colitis & Crohn's disease. remission in up to 80% of patients.

Note: Methotrexate Antimetabolite that has beneficial effects in a number of chronic inflammatory diseases, including crohn's disease and rheumatoid arthritis

Anti-Tumor Necrosis Factor

Infliximab

- A chimeric mouse-human monoclonal antibody to human TNF-α
- Infliximab is used in the acute and chronic treatment of patients with moderate to severe Crohn's disease and ulcerative colitis