GI Pharmacology

Dr. Alia Shatanawi

10-04-2018
GastroEsophageal Reflux Disease

- Heartburn; Dysphagia; chronic symptoms or mucosal damage produced by abnormal reflux of gastric contents into the esophagus.
- 10% of US population.
- Therapy based on decreasing acidity, increasing lower esophageal sphincter tone; enhanced clearance of refluxed material.
GastroEsophageal Reflux Disease

Treatment:

1. PPIs.
2. Coating agents
   Sulcralfate (Carafate) coats mucous membranes and sores to provide an additional protective barrier against stomach acid.
3. Promotility/prokinetic agents: help tighten the lower esophageal sphincter and promote faster emptying of the stomach.
   - Metoclopramide
   - Bethanechol.

- Health care providers often are reluctant to prescribe promotility agents because they have fairly significant side effects.
- Promotility agents also do not work as well as PPIs for most people.
Drugs Affecting GI Motility

• Drugs Stimulating GI Motility
  “Prokinetic Agents”

• Laxative Agents.

• Antidiarrheal Agents.
Drugs Stimulating GI Motility
”Prokinetic Agents”

Potential Uses:

- Lower esophagaeal sphincter: GERD.
- Stomach: gastroparesis and postsurgical gastric emptying delay.
- Small intestine: Postoperative ileus.
- Colon: constipation.
Prokinetic Agents

Cholinomimetic Agents:

Bethanecol:

Stimulates $M_3$ receptors on muscle cells and myenteric plexus synapses.

Was used in GERD and gastroparesis.

Neostigmine:

$\text{AChase}$ inhibitor.

"Acute Colonic Pseudo-obstruction (Ogilvie’s syndrome)”: IV can result in rapid evacuation of flatus and feces.

Can cause cholinergic effects.
Prokinetic Agents

Dopamine Receptor Antagonists:
- Metoclopramide
- Domperidone.

$D_2$ antagonists.

Dopamine inhibits cholinergic action on smooth muscle.

Have actions on esophagus and stomach, but not the small or large intestine.

Also inhibit the chemoreceptor trigger Zone (Area Postrema).
Prokinetic Agents

Dopamine Receptor Antagonists:

1. GERD:
   Not effective with erosive esophagitis.
   Not superior to antisecretory agents.
   Used in combination with antisecretory drugs.

2. Gastroparesis:
   Postsurgical: vagotomy and antrectomy.
   Diabetic.
   Advancement of feeding nasoenteric tubes.
Prokinetic Agents

Dopamine Receptor Antagonists:

3. Nonulcer dyspepsia.
4. Antiemetic agents.
5. Postpartum lactation stimulation.
Prokinetic Agents

Dopamine Receptor Antagonists:

Adverse Effects:

Metclopramide crosses BBB so can cause:

Restlessness, drowsiness, insomnia, anxiety, agitation, extrapyramidal symptoms (dystonias, akathisia, parkinsonian features, Tardive dyskinesia)

Domperidone does not cross the BBB, so does not cause CNS effects

Both drugs can elevate serum prolactin levels causing galactorrhea, gynecomastia, impotence and menstrual disorders.
Prokinetic Agents

Macrolide Antibiotics:
Directly stimulate motilin receptors in the GIT.
Gastroparesis: given IV, but tolerance develops rapidly.
Acute upper GIT bleeding: to promote emptying of blood before endoscopy.
Prokinetic Agents

Chloride Channel Activator:

**Lubiprostone:**
PG analog.
Can be used in chronic constipation.
Stimulates chloride channel opening in GIT.
This increases liquid secretion in the intestine.
Delays gastric emptying leading to nausea.
Constipation

- Often caused by a lazy colon or a spastic colon that remains contracted for a prolonged time.
- Other conditions that can produce a sluggish, poorly contracting bowel include: pregnancy, certain drugs, thyroid hormone deficiency, travel, stress, and the chronic abuse of laxatives.
Laxatives

**Bulk-Forming Laxatives:**
- Are indigestible, hydrophilic colloids that absorb water, forming a bulky, emollient gel that distends the colon and promotes peristalsis.
- Can cause bloating and flatus.
- **Natural Plant Products:**
  - Psyllium.
  - Sterculia "Normacol"
  - Methylcellulose.
- **Synthetic Fibers:**
  - Polycarbophil.
Bulk laxatives

Cellulose, agar-agar, bran, linseed
Laxatives

Stool Surfactant Agents (Softeners):

- They permit water and lipids to penetrate.
- Given orally or rectally.
- **Docusate.**
- **Glycerin suppository.**
- **Mineral oil:**
  - Clear viscous oil that lubricates fecal material, retarding water absorption from the stool.
  - Used to prevent and treat fecal impaction.
  - Aspiration can cause lipoid pneumonia.
  - Can impair absorption of fat-soluble vitamins.
Laxatives

Osmotic Laxatives (Purgatives):

- Soluble nonabsorbable compounds that result in increased stool liquidity due to an obligate increase in fecal fluid.

- Magnesium oxide (Milk of Magnesia):
  - Can cause hypermagnesemia.
  - Large doses of magnesium citrate and sodium phosphate can cause **Purgation**: rapid bowel evacuation within 1-3 hours. This might cause volume depletion.
Laxatives

Osmotic Laxatives:
- Sorbitol.
- Lactulose.
  - Sugars metabolized by bacteria producing severe flatus and cramps.
Laxatives

Osmotic Laxatives:

- **Balanced Polyethylene Glycol:**
  - Safe solution: no intravascular fluid or electrolyte shifts. Does not cause cramps or flatus.
  - Used for complete colonic cleansing before endoscopy.
  - PEG is an inert, nonabsorbable, osmotically active sugar.
  - Sodium sulfate, chloride, bicarbonate and potassium chloride.
  - For colonic cleansing, it should be ingested rapidly (4 L over 2-4hs).
  - For chronic constipation, PEG powder is mixed with water or juice.
Laxatives

Stimulant Laxatives (Cathartics):

- Direct stimulation of the enteric system.
- Colonic electrolyte and fluid secretion.
- Can lead to dependence and destruction of the myenteric plexus resulting in colonic atony and dilation.
- May be needed in neurologically impaired patients and in bed-bound patients in long term care facilities.
A. Stimulation of peristalsis by mucosal irritation
Laxatives

Stimulant Laxatives (Cathartics):

- Anthraquinone Derivatives:
  - Aloe.
  - Senna.
  - Cascara.
    - Poorly absorbed.
    - After hydrolysis, produce bowel movement in (6-12) hours.
    - Cause brown pigmentation of the colon” Melanosis Coli”. 
    - Not carcinogenic.
Laxatives

- **Stimulant Laxatives (Cathartics):**
  - **Castor Oil:**
    - Hydrolyzed in upper intestine into ricinoleic acid which is a local irritant.
    - Was used as purgative to clean the colon before procedures.
Laxatives

Tegaseroid:

- Is a serotonin 5-HT\textsubscript{4} partial agonist, which are presynaptic receptors of the submucosal intrinsic primary afferent nerves which enhance the release of their neurotransmitters.
- These neurones stimulate proximal bowel contraction (via ACh and substance P) and distal relaxation (via nitric oxide and VIP).
- The drug promotes gastric emptying and small and large bowel transit but has no effect on esophageal motility.
- Also stimulates cAMP-dependent chloride secretion leading to increased stool liquidity.
Laxatives

Tegaseroid:

Clinical Uses:
- Chronic constipation.
- Nonulcer dyspepsia.
- Gastroparesis.
- Irritable bowel syndrome.
Laxatives

Tegaseroid:

Adverse Effects:

Extremely safe drug.
Diarrhea occurs in 9% of patients but resolves within days.
Expensive.
Antidiarrheal Agents

Can be used in mild to moderate acute diarrhea.

Should not be used in the presence of infective diarrhea.

Can be used to control chronic diarrhea, like in irritable bowel syndrome or inflammatory bowel disease.
A. Antidiarrheals and their sites of action
Antidiarrheal Agents

Opioid Agonists:
Have significant constipating effects:
Inhibit presynaptic cholinergic nerves, leading to increased colonic transit time and increased fecal water absorption.
Decrease mass colonic movements and gastrocolic reflex.
Can have CNS effects and addiction potential.
Usually combined with atropine to reduce dependence.
Antidiarrheal Agents

Opioid Agonists:

Loperamide:

Does not cross BBB.
No analgesic or addiction potential.

Diphenoxylate:

Can have CNS effects and dependence.
Antidiarrheal Agents

Kaolin and Pectin:

Kaolin is a naturally occurring hydrated magnesium silicate.
Pectin is an indigestible carbohydrate derived from apples.

Both act to absorb bacteria, toxins and fluid.
Usually combined, e.g. Kaopectate.
Taken far from other medications.
Antidiarrheal Agents

Bile salt-binding resins:
- Cholestyramine
- Colistipol.

Malabsorption of bile salts (e.g., after surgical resection), can cause diarrhea. The drugs can bind bile salts. Can cause bloating, flatulence, constipation and fecal impaction. Also, drug and fat malabsorption.
Antidiarrheal Agents

Octreotide:
Is a synthetic octapeptide with actions similar to somatostatin.

Somatostatin is a 14 amino acid peptide released in the GIT and pancreas as well as from the hypothalamus:
1. Inhibits release of many hormones.
2. Reduces intestinal fluid and pancreatic secretions.
3. Slows GIT motility and gallbladder contraction.
5. Inhibits secretion of some anterior pituitary hormones.
Antidiarrheal Agents

Octreotide:

Clinical Uses:

1. Inhibition of endocrine tumor effects:
   Carcinoid and VIPoma can cause secretory diarrhea and systemic symptoms like flushing and wheezing.

2. Diarrhea due to vagotomy or dumping syndrome or short bowel syndrome and AIDS.

3. In small doses can stimulate motility in small bowel bacterial overgrowth or intestinal pseudo-obstruction secondary to scleroderma.

4. Pancreatic fistula, pituitary tumors and GI bleeding.
Antidiarrheal Agents

Octreotide:

Adverse Effects:

- Steatorrhoea which can cause fat-soluble vitamin deficiency.
- Nausea, pain, flatulence.
- Sludge or gall stones.
- Hyper or hypoglycemia due to hormonal imbalance.
- Hypothyroidism.
- Bradycardia.
Know the Signs of TD

Symptoms May Range from Mild to Severe

- **Movements of the Mouth**
  - Such as frowning, sticking out tongue, lip smacking, puckering, and pursing

- **Rapid Movements of the Body**
  - Commonly in the arms, legs, and trunk

- **Face**
  - Disfigured facial features such as drooping of the mouth or eyes

- **Eyes**
  - Rapid blinking

- **Difficulty Breathing**

- **Difficulty Swallowing**

- **Difficulty Speaking**

**Sources**
Laxatives

• Drugs taken to induce bowel movements or loosen the stool: increase fecal water loss.
• All laxatives convert the intestine from primarily an absorbing organ for water and electrolytes to primarily a secreting organ.

Laxative classification:

1. Bulk-forming agents: Fiber, Bran
2. Stool softeners: Docusate,
3. Lubricants: Mineral oil
4. Stimulants: Diphenylmethanes (bisacodyl), Castor oil
5. Osmotic laxatives: Mg\(^{2+}\) salts, Lactulose (Cephulac), Glycerin suppositories.
Psyllium (Metamucil), Methylcellulose (Citrucel)  
Fiber, Bran,

- Effective within 1-3 days.
- Cause the stool to be bulkier and retain more water, forms an emollient gel.
- Be taken with plenty of water.
- Gentlest of the laxatives.
- Side effects: Very few; minimal systemic effects; can bind drugs and prevent intestinal absorption; may contain high amounts of sodium which is absorbed; some preparations have high dextrose content; patients with pre-existing GI disease should avoid.
Stool softeners

- Docusate, dehydrocholic acid.

- Detergents or surfactants that act as stool-wetting and stool-softening agents, allowing the mixing of water, lipids, and fecal matter.

- Alters intestinal permeability and increases net water and electrolyte secretions in the intestine.

- Softening of feces within 1-3 days to prevent straining.
Lubricant/Emollient

- Site of Action: Colon.
- Onset of Action: 6 - 8 hours.
- These simply make the stool slippery, so that it slides through the intestine more easily. An example is mineral oil, which also retards colonic absorption of water, softening the stool.
- Mineral oil may decrease the absorption of lipid-soluble vitamins (A, D, E, and K).
- not recommended for regular use.
Stimulant laxatives

Diphenylmethanes (bisacodyl), Castor oil

- Stimulate intestinal motility; promote accumulation of water and electrolytes in the colonic lumen; may inhibit intestinal Na⁺,K⁺-ATPase, some may increase synthesis of prostaglandins and cyclic AMP.

- Common side-effects:
  - nausea
  - abdominal cramps
  - vomiting
  - rectal sensation burning

- Serious side-effects:
  - electrolyte imbalance (long-term use)
  - cathartic colon (long-term use)

- The most severe laxative, must be used with great caution
Osmotic laxatives

1. Magnesium salts \(\text{MgSO}_4, \text{Mg(OH)}_2, \text{MgCitrate}\), sodium salts \{mixture of sodium mono- and di-basic phosphate\}:
   - Poorly absorbed and remain in the bowel causing water retention. Accumulation of \(\text{Mg}^{2+}\) can occur with impaired renal function. Sodium load can be a problem with impaired renal function or congestive heart failure.
   - Produce a watery evacuation within 1-3 hours after oral administration. Useful prior to surgical, radiological, and endoscopic procedures.
2. Glycerin suppositories, Sorbitol, Lactulose (Cephulac), polyethylene glycol (PEG):

- Lactulose (Cephulac) {disaccharide of fructose-lactose} is not broken down by small intestine or pancreatic enzymes, but cleaved by colonic bacterial enzymes.
- Produces softening of stool over several days.
- Common side effects are abdominal cramping, gas, borborygmus, flatulence.
- Solutions of PEG and electrolytes (NaCl, NaCO₃, KCl) are used for “whole bowel irrigation” to prepare the bowel for surgery or colonoscopy: GoLytely, GlycoLax, CoLyte, NuLytely.
Diarrhea

- **Secretory diarrhea**: an increase in the active secretion or an inhibition of absorption. The most common cause of this type of diarrhea is a cholera toxin that stimulates the secretion of anions, especially chloride ions. Therefore, to maintain a charge balance in the lumen, sodium is carried with it, along with water.

- **Osmotic diarrhea**: loss of water due to a heavy osmotic load. This can occur when there is maldigestion, where the nutrients are left in the lumen, which pulls water into the lumen.

- **Motility-related diarrhea**: GI motility is abnormally high not leaving enough time for sufficient nutrients and water to be absorbed.

- **Inflammatory diarrhea**: damage to the mucosal lining or brush border, which leads to a passive loss of protein-rich fluids, and a decreased ability to absorb these lost fluids. Features of all three of the other types of diarrhea can be found in this type of diarrhea. It can be caused by bacterial infections, viral infections, parasitic infections, or autoimmune problems such as inflammatory bowel disease.
Management of diarrhea

- Eliminate the cause and replace fluid and electrolytes.
- Adults should consume broth, soup, fruit juices, soft fruits, or vegetables.
- Children should drink a special liquid with nutrients.
- If a food or medicine is the cause, avoid it.
- Avoid milk products, high-fat or greasy foods, sweet foods.
- As the patients feel better, eating soft, bland food.
Antisecretory and antimotility: Opiates

**Loperamide**, a synthetic piperidine derivative (Imodium)
- Agonist of μ-opioid receptors in the large intestines.
- It penetrates the CNS poorly and does not affect the CNS.
- Decreases activity of the intestinal wall.
- In combination with antimicrobials is effective in controlling symptoms of traveler’s diarrhea.

**Diphenoxylate**, little opioid-like effects in therapeutic range; Potentially habit-forming, therefore manufactured and marketed as a combination drug with atropine to discourage abuse (Lomotil).

Side effects: drowsiness, constipation, abdominal pain or discomfort, dry mouth, fatigue, and in rare cases toxic megacolon, mild euphoria and mild stimulation.
Blocking toxin: Adsorbents

• Forming coating along the lining of the GI tract and adsorbing bacterial and toxic products.

• Bismuth subsalicylate (Pepto-Bismol)
  – may exert antidiarrheal action not only by stimulating absorption of fluid and electrolytes across the intestinal wall and by inhibiting synthesis of PG responsible for intestinal inflammation and hypermotility.

• Cholestyramine (Questran).
Rehydration therapy: Oral

- Pedialyte, Rehydralyte.
- Ingestion of soft easily digested foods and/or noncarbonated beverages such as fruit juices.
- Uptake of glucose and amino acids by enterocytes is accompanied by uptake of sodium; chloride, and water follow. Thus, dehydration can be prevented or treated by providing readily absorbed sugars and amino acids that enhance the absorption of water by the small intestine.