Antidiarrheals and laxatives

Diarrhea

Acute diarrhea

- sudden onset in a previously healthy person
- lasts from 3 days to 2 weeks
- self-limiting
- resolves without sequelae

Diarrhea (cont'd)

Chronic diarrhea

- **lasts for more than 3 weeks**
- **associated with recurring passage of diarrheal stools, fever, loss of appetite, nausea, vomiting, weight loss, and chronic weakness**

Causes of Diarrhea

Acute diarrhea

bacterial

viral

drug induced

nutritional

protozoal

Chronic diarrhea

tumors

diabetes

Addison's disease

hyperthyroidism

irritable bowel syndrome

Antidiarrheals: mechanism of action

Adsorbents

- coat the walls of the GI tract
- bind to the causative bacteria or toxin, which is then eliminated through the stool
- examples: bismuth subsalicylate, kaolin-pectin, activated charcoal

Antidiarrheals: mechanism of action (cont'd)

Anticholinergics

- decrease intestinal muscle tone and peristalsis of GI tract
- result: slowing the movement of fecal matter through the GI tract
- examples: belladonna alkaloids, atropine, hyoscyamine

Antidiarrheals: mechanism of action (cont'd)

Opioids

- decrease bowel motility
- decrease transit time through the bowel, allowing more time for water and electrolytes to be absorbed
- opioids are effective in the treatment of moderate-to-severe diarrhea!
- examples: opium tincture, loperamide, diphenoxylate

Opioids (cont'd)

- ***diphenoxylate*** **is about an order of magnitude more potent than morphine**
- ***loperamide*** **acts predominantly on μ receptors in the GI tract, it is 40 to 50 times more potent than morphine; penetrates the CNS very poorly**
- **can be given alone or in combination with antimicrobials (trimethoprim, trimethoprim-sulfamethoxazole, fluoroquinolones)**

Antidiarrheals: mechanism of action (cont'd)

Octreotide, the synthetic analog of ***somatostatin***

1. ↓ of gastric acid and pepsinogen secretion
2. ↓ of intestinal fluid and bicarbonate secretion
3. ↓ of smooth muscle contractility

- must be administered parenterally
- it is useful in treating the symptoms of tumors of the GI tract (carcinoid, VIPoma, glucagonoma, gastrinoma, insulinoma)
- diarrhea refractory to other treatment (*e.g.*, AIDS-related diarrhea)

Antidiarrheals: mechanism of action (cont'd)

Intestinal flora modifiers

- bacterial cultures of *Lactobacillus* organisms work by:
  - supplying missing bacteria to the GI tract
  - suppressing the growth of diarrhea-causing bacteria
- example: *L. acidophilus*

Antidiarrheal agents: side effects

Adsorbents

- constipation, dark stools
- confusion, twitching
- hearing loss, tinnitus, metallic taste, blue gums

Antidiarrheal agents: side effects (cont'd)

Anticholinergics

- urinary retention, dry mouth
- headache, dizziness, confusion, anxiety, drowsiness
- dry skin, rash, flushing
- blurred vision, photophobia, increased intraocular pressure
- hypo-, hypertension, brady-, tachycardia

Antidiarrheal agents: side effects (cont'd)

Opiates

- drowsiness, sedation, dizziness, lethargy
- nausea, vomiting, anorexia, constipation
- respiratory depression
- bradycardia, palpitations, hypotension
- urinary retention
- flushing, rash, urticaria

Antidiarrheal Agents: Interactions

- adsorbents decrease the absorption of many agents, including digoxin, clindamycin, quinidine, and hypoglycemic agents
- antacids can decrease effects of anticholinergic antidiarrheal agents

Laxatives

Constipation

- abnormally infrequent and difficult passage of feces through the lower GI tract
- symptom, not a disease
- disorder of movement through the colon and/or rectum
- can be caused by a variety of diseases or drugs

Laxatives: Mechanism of Action

a) retention of fluid in colonic contents, thereby:

- **increasing bulk and softness**
- **facilitating transit**

b) direct and indirect decrease of net absorption of water and NaCl

c) increased intestinal motility, causing:

- **decreased absorption of salt and water**
- **decreased transit time**

Laxatives: Mechanism of Action

bulk forming

emollient

hyperosmotic

saline

stimulant

Laxatives: mechanism of action (cont'd)

Dietary fiber and bulk forming

- high fiber
- absorbs water to increase bulk
- distends bowel to initiate reflex bowel activity
- examples:
  - psyllium, carboxymethylcellulose
  - dextrose, plant gums

Laxatives: Mechanism of Action (cont'd)

Emollient

- stool softeners and lubricants
- promote more water and fat in the stools
- lubricate the fecal material and intestinal walls
- examples:
  - stool softeners: docusate salts
  - lubricants: mineral oil

Laxatives: Mechanism of Action (cont'd)

Hyperosmotic

- increase fecal water content
- result: bowel distention, increased peristalsis, and evacuation
- examples:
  - polyethylene, glycol sorbitol
  - glycerin, lactulose

Laxatives: Mechanism of Action (cont'd)

Saline

- increase osmotic pressure within the intestinal tract, causing more water to enter the intestines
- result: bowel distention, increased peristalsis, and evacuation
- examples:
  - magnesium sulfate, magnesium hydroxide
  - magnesium citrate, sodium phosphate

Laxatives:
Mechanism of Action (cont'd)

Stimulants

- increases peristalsis via intestinal nerve stimulation
- examples:
  - castor oil, senna
  - Cascara, bisacodyl, phenolphthalein

Laxatives: Indications

Laxative Group	
Bulk forming	❑ acute and chronic constipation ❑ irritable bowel syndrome ❑ diverticulosis ❑ acute and chronic constipation
Emollient	❑ softening of fecal impaction

Laxatives: Indications (cont'd)

Laxative Group	
Hyperosmotic	❑ chronic constipation ❑ diagnostic and surgical preparation ❑ constipation
Saline	❑ diagnostic and surgical preparation ❑ removal of helminths and parasites

Laxatives: Indications (cont'd)

Laxative Group	
Stimulant	❑ acute constipation ❑ diagnostic and surgical bowel preparation

Laxatives: Side Effects

Bulk-forming laxatives have few side effects and minimal systemic effects:

- **allergic reactions (*plant gums*)**
- **flatulence**
- **systemic retention of Na^+ and H_2O *(psyllium, carboxymethylcellulose)***
- ***dextrose* should be avoided in diabetic patients**
- ***cellulose* can reduce the absorption of many drugs**

(cardiac glycosides, salicylates, nitrofurantoin)

- ***psyllium* may bind coumarin derivatives**

Laxatives: Side Effects (cont'd)

Saline laxatives

- up to 20% of the salt is absorbed
- Mg^{2+} - toxicity in patients with impaired renal function
- Na^{+} salts should not be used in patients with CHF or renal disease
- phosphate laxatives can cause hyperphosphatemia and a reduction of plasma Ca^{2+}
- hypertonic salt solutions can produce significant dehydration and must be administered with sufficient water to ensure that no net loss of body water occurs

Laxatives: Side Effects (cont'd)

Hyperosmotic

- ***lactulose:*** flatulence, cramps, abdominal discomfort
- excessive dosage can cause diarrhea, loss of fluid and K^+, hypernatremia, exacerbation of hepatic encephalopathy

Contraindications

- patients requiring a galactose-free diet must not use ***lactulose***
- patients with diabetes must be cautious in using ***lactulose***

Stimulants

- fluid and electrolyte deficits (overdosage)
- they can damage enterocytes (inflammatory response in the colon)
- allergic reactions, osteomalacia
- protein- losing gastroenteropathy
- possible pink coloring of the urine and feces *(phenolphthalein)*
- *an excessive laxative effect and abdominal pain (senna, cascara)*

All laxatives can cause electrolyte imbalances!

Prokinetic agents

Mechanisms of action

- direct M_2-receptor agonists ***(bethanechol)***
- AChE inhibitors ***(neostigmine)***
- inhibitory presynaptic D_2-receptor blockers ***(metoclopramide)***
- excitatory presynaptic 5-HT_4-receptor agonists ***(cisaprid)***
- excitatory motilin receptor activators ***(erythromycin)***

Clinical usefulness

- prokinetic drugs increase gastric emptying
- they increase tone of the lower esophageal sphincter
- they exhibit antiemetic activity ***(metoclopramide)***
- they improve coordination of gastroduodenal contractions

Adverse effects

- cholinergic agonists have variety of muscarinic side effects (excess GI secretions, cramps, salivation, sweating, urination, lacrimation, defecation)
- dopamine-receptor antagonists can induce dystonia, parkinsonism, hyperprolactinemia (gynecomastia, galactorhea)