DRUGS AFFECTING THE MOTILITY OF THE GASTROINTESTINAL TRACT

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Course: Basic Therapeutics
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EXPECTATIONS...???
QUIZ TIME!
1. What are the Causes of constipation..?
2. Mention three drugs used for treatment of constipation..?
3. What do we mean by purgatives..?
4. Mention two drugs used for treatment of diarrhoea..?
5. What is the mechanism of action of lopremide..?
OBJECTIVES:

By the end of this lecture student should be able to:

1. Explain the mechanisms by which constipation and diarrhoea are developed.

2. Mention the different types of drugs used in treatment of constipation and diarrhoea.
Drugs that alter the motility of the gastrointestinal tract include:

1) Purgatives, which accelerate the passage of food through the intestine.

2) Agents that increase the motility of the gastrointestinal smooth muscle without causing purgation.

3) Antidiarrhoeal drugs, which decrease motility.

4) Antispasmodic drugs, which decrease smooth muscle tone.
Constipation

**Definition:**

Chronic constipation is a disorder characterized by unsatisfactory defecation that results from infrequent stools, difficult stool passage, or both over a time period of at least 12 weeks.
Causes of constipation

1. In most cases of chronic constipation, no specific cause is found (chronic idiopathic constipation)

2. Lifestyle Factors
   a) Inadequate fluid intake
   b) Decreased food intake
   c) Inappropriate bowel habits
   d) Immobility
Causes of constipation

3. Medications

4. Endocrine and Metabolic disorders
   a) Hypothyroidism
   b) Hypercalcemia
   c) Hypokalemia
   d) Pheochromocytoma
Causes of constipation

5. Neurologic
   a) Parkinson's disease
   b) Multiple sclerosis
   c) Spinal lesions
   d) Damage to sacral parasympathetic nerves
   e) Autonomic neuropathy (Diabetes mellitus)

6. Psychological
   a) Depression
   b) Eating disorders (e.g., anorexia nervosa)
Causes of constipation

7. GI disorders:
   a) Irritable bowel syndrome
   b) Hemorrhoids and anal fissures
   c) Tumors
   d) Hernia

8. Pregnancy
Drugs causing constipation

1) NSAIDs (inhibit prostaglandin synthesis)
2) Opiates: Orally administered opiates have greater inhibitory effect than parenterally administered agents
3) Anticholinergics
4) Antihistamines
5) Antiparkinsonian agents (e.g., benztropine or trihexyphenidyl)
6) Phenothiazines
7) Tricyclic antidepressants
8) Antacids containing calcium carbonate or aluminum hydroxide
9) Barium sulfate.
10) Calcium channel blockers
11) Clonidine.
12) Diuretics (nonpotassium-sparing)
13) Ganglionic blockers
14) Iron preparations
15) Muscle blockers (D-tubocurarine, succinylcholine)
Mechanism of drug-induced constipation

1. **Drugs with anticholinergic action**
   (e.g. first generation antihistaminic drugs, tricyclic antidepressants, benztropine, phenothiazines,..)

   GIT motility is under parasympathetic (cholinergic) control. Parasympathetic stimulation → ↑motility

   Drugs with anti-cholinergic effect (whether it is their main action or a side effect) → ↓motility → constipation
Mechanism of drug-induced constipation

2. Opioids:

Opioids cause constipation by:

A) Increasing the smooth muscle tone, suppressing forward peristalsis, raising sphincter tone at the ileo-cecal valve and anal sphincter. This delays passage of feces through the GIT → increase in absorption of electrolytes and water in the small intestine and colon → constipation

B) Reducing sensitivity to rectal distension.
Mechanism of drug-induced constipation

3. Electrolyte disturbance as hypokalemia or hypercalcemia.

4. Laxative abuse (leads to atonic intestine).
Treatment of constipation

**General measures:**

1) Increase the amount of *fiber* consumed: daily fruits, vegetables, bran and cereals).

**Definition:** Fiber is that part of food that resists enzymatic digestion

**Effect of fiber:** Fiber reaches the colon unchanged.

- Colonic bacteria → Fermentation →
  - Short-chain fatty acids (→ prokinetic effect)
  - Increased bacterial mass (→ increased stool bulk).
- Fiber that is not fermented → osmotic effect → increases stool bulk.
2. Increasing **fluid** intake.
3. Regulation of bowel habits.
4. Regular exercise.
5. Treatment of the cause
6. For drug causes of constipation, a non constipating alternatives should be used. If no alternatives exist, lower the dose.
If general measures alone are inadequate or not applicable (e.g., because of old age), they may be supplemented with bulk-forming agents, osmotic laxatives or stimulant laxatives.
## Definitions

<table>
<thead>
<tr>
<th>Laxatives</th>
<th>Cathartics</th>
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<tbody>
<tr>
<td>Drugs that help evacuation of formed fecal material from the rectum</td>
<td>Drugs that help evacuation of unformed, usually watery fecal material from the entire colon.</td>
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Classification of laxatives

1. Bulk-forming laxatives.
2. Stimulant laxatives.
3. Osmotic laxatives.
4. Emollient laxatives (fecal softeners).
5. Lubricants.
1- Bulk-forming agents

**Drugs:**

1. Methylcellulose
2. Bran
3. Psyllium
   - taken as granules, powders or tablets.
   - active after 12-36h.
Mechanism of action of bulk-forming agents:

They increase stool bulk and water content (make stools **bulky** → stimulate peristalsis) and **soft** → easy to pass) (**similar to natural fiber**)
Indications:
1. They are the first-line treatment of constipation.
2. Conditions where dietary intake of fibers cannot be increased.

Precautions:
- Adequate fluid intake to avoid intestinal obstruction.

Adverse effects of bulk-forming laxatives:
1. Abdominal distension (due to fermentation).
2. Intestinal obstruction when not consumed with sufficient fluid.

Contraindications:
1. Atony of the colon.
2. Intestinal obstruction.
3. Immobility.
2. Stimulant (irritant) laxatives

**Dosage forms:**

<table>
<thead>
<tr>
<th>Substance</th>
<th>Form</th>
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<tr>
<td>Bisacodyl</td>
<td>Oral and rectal suppository</td>
</tr>
<tr>
<td>Sodium picosulfate</td>
<td>Oral</td>
</tr>
<tr>
<td>Senna and Cascara</td>
<td>Oral</td>
</tr>
<tr>
<td>Castor oil</td>
<td>Oral</td>
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Mechanism of action of stimulant agents:

• They are given in an inactive form → hydrolyzed in the GIT into active forms → GIT irritation → modify permeability of the mucosal cells → ↑ fluid and electrolyte secretion in the GIT → distension → evacuation of soft (or liquid) bulky stools.

• They probably cause direct stimulation of the enteric nerves.
According to the site of GIT irritation they are classified into:

1. Small bowel irritant (hydrolyzed in the small intestine by the action of lipases): castor oil
2. Large bowel irritants (hydrolyzed by colonic bacteria):
   a) Bisacodyl and Sodium picosulfate
   b) Senna and Cascara
**Indications of large bowel irritants:**

1. Prevention of straining at stool following surgery, myocardial infarction or stroke
2. Painful diseases of the anus, e.g., fissure or hemorrhoids.
3- Osmotic laxatives

1. **Saline laxatives**
   (have cathartic action in large doses)
   A. Magnesium salts (sulfate, hydroxide or citrate).
   B. Sodium phosphate.
Mechanism of action:

1. Poorly absorbed → water retention (osmotic effect) → soft bulky stools → ↑peristalsis → relief of constipation

2. Magnesium-containing laxatives may stimulate the release of cholecystokinin, which leads to intraluminal fluid and electrolyte accumulation and to increased intestinal motility
**Uses:**

- Enema (causes bowel evacuation after 30 min)
- Oral forms (cause bowel evacuation after 2-5h)

Both forms are used for intestinal evacuation before abdominal radiological procedures, sigmoidoscopy or surgery (cathartics)
Adverse effects:
1. Flatulence, abdominal cramps, diarrhea
2. Intravascular volume depletion
3. Electrolyte disturbances

Contraindications:
1. Renal insufficiency
2. Severe cardiac disease
3. Preexisting electrolyte abnormalities
4. Patients on diuretic therapy
2. Non-digestible sugars and alcohols

1. Lactulose (disaccharide of galactose and fructose that resists intestinal disaccharidase activity)
2. Sorbitol (monosaccharide)
**Mechanism of action:**
Lactulose $→$ metabolized by colonic bacteria into short chain fatty acids $→$ osmotic effect.

**Adverse effects:**
1. Abdominal distention
2. Diarrhea

**Mechanism of action:**
Poorly absorbed, and retained in the lumen of the gut $\Rightarrow$ osmotic effect $\Rightarrow$ increase water content of stools.
4. Glycerin

**Dosage form:**
Suppository (laxative effect > 30 min.)

**Mechanism of action:**
- Osmotic effect in the rectum.

**Adverse effects:**
Occasional rectal irritation.

**Uses:**
Intermittent constipation in children.
4- Fecal softeners/emollient laxatives

1. Docusate salts (sodium or calcium) (weak laxatives)

**Mechanism of action:**
1. Reduces surface tension of stools → increases penetration of fluids into feces → soft bulky stools
2. Stimulate intestinal fluid and electrolyte secretion (by altering mucosal permeability)

**Dosage forms:**
1. Oral form (active within 1-3 d)
2. Rectal form has a rapid onset of action but is contraindicated in hemorrhoids and anal fissure.
2. **Mineral oil:**

**Mechanism of action:**

1. Indigestible and with minimal absorption. Coat stool and allow easier passage.
2. Inhibit colonic absorption of water $\rightarrow$ increasing stool weight and decrease stool transit time.

**Dosage forms:**

Oral or rectal. Laxative effect is noted after 2 or 3 days of oral use.
New agents

**Lubiprostone**

**Mechanism of action:**
Opening of chloride channels locally in the GI luminal epithelium, which stimulates chloride-rich intestinal fluid secretion and shortens GI transit time

**Uses:**
Chronic idiopathic constipation in adults

**Adverse effects:**
1. Headache
2. Diarrhea, and nausea, as a result of delayed gastric emptying.
Laxative abuse syndrome

**Mechanism:**
1. With the use of strong purgatives, the colon may be so thoroughly evacuated that a bowel movement may not occur normally until a few days later. This delay reinforces the need for more laxative. Eventually the patient may require daily laxatives to maintain bowel function.
Laxative abuse syndrome (cont.)

Mechanism:

2. 

- Bowel inertia
- Hypokalemia
- "Constipation"
- Laxative
- Enteral loss of $K^+$
- Renal loss of $K^+$
- Renal retention of $Na^+$, $H_2O$
- Aldosterone
- $Na^+$, $H_2O$
Laxative abuse syndrome

- Reduction of defecation reflex
- Constipation
- Loss of potassium
- Laxative intake
- Loss of sodium and water
- Increase in aldosterone secretion
Diarrhea

**Definition:**
diarrhea is an increased frequency and decreased consistency of fecal discharge as compared to an individual’s normal bowel pattern.

**Classification:**
- Acute <14 d
- Persistent >14 d
- Chronic > 30 d
Causes of diarrhea

1. Infectious (viral or bacterial)
2. Non infectious
Drugs causing diarrhea

1) Laxatives
2) Antacids containing magnesium
3) Antineoplastic drugs
4) Antibiotics
   a) Clindamycin
   b) Tetracyclines
   c) Sulfonamides
   d) Any broad-spectrum antibiotic
5) Antihypertensives
   a) Methyldopa
   b) Angiotensin-converting enzyme inhibitors
   c) Angiotensin receptor blockers
   d) α-adrenergic receptor blockers
6) Cholinergic drugs
   1. Neostigmine

7) Cardiac agents
   1. Quinidine
   2. Digoxin

8) Non-steroidal anti-inflammatory drugs

9) Misoprostol

10) Proton pump inhibitors

11) H2-receptor blockers
Treatment of diarrhea

Non-pharmacologic therapy:

Dietary management:

1. Discontinue consumption of solid foods and dairy products for 24 h (valuable in osmotic diarrhea)
2. For patients who are experiencing nausea and/or vomiting, a mild, digestible, low-residue diet should be administered for 24 hours.
3. If vomiting is present and uncontrollable with antiemetics, nothing is taken by mouth. As bowel movements decrease, a planed diet is begun.

Rehydration and maintenance of water and electrolytes
Treatment of dehydration

- Increase fluid intake (fruit juice – contain glucose and potassium)
- Oral rehydration solution (ORS). The WHO formula contains glucose, sodium, potassium, chloride and bicarbonate in an isotonic fluid.
Antidiarrhoeal agents

**Indications of antidiarrhoeal agents:**
1. Patients with mild to moderate acute diarrhea
2. Control chronic diarrhea caused by IBS or IBD

**Contraindications:**
Patients with bloody diarrhea, fever or systemic toxicity (risk of worsening of the underlying condition)

**Discontinued** in patients whose diarrhea is worsening despite therapy
Treatment of diarrhea

**Pharmacologic therapy:**

Drugs used for the treatment of diarrhea include

1. Antimotility agents
2. Adsorbents
3. Antisecretory compounds
4. Antibiotics
5. Enzymes
6. Intestinal microflora.
Antimotility agents (Opioids)

**Opioids agonists:**

**Action in the GIT** (mediated by binding to opioid receptors)

1. Increase segmentation and a decrease propulsive movement → ↑ intestinal transit time → ↑ absorption of water and electrolyte → feces become more solid

2. Antisecretory

3. ↑ tone of the internal anal sphincter

4. ↓ response to the stimulus of a full rectum (by their central action)
Opioids - Diphenoxylate

Opioid agonist that has no analgesic properties in standard doses. Higher doses have central opioid actions. Used in combination with a subtherapeutic dose of atropine (to prevent abuse)

**Contraindications:**
1. Children below 2 y (toxicity at lower doses than adults)
2. Obstructive jaundice

**Drug interactions:**
1. Potentiate the effects of CNS depressants
2. Co-administration with MAO inhibitors → hypertensive crises

**Adverse effects:**
1. Caused by the atropine in the preparation and include anorexia, nausea, pruritus, dizziness, and numbness of the extremities.
2. Prolonged use of high doses may cause dependence
Opioids - Loperamide

Opioid agonist that does not cross the blood-brain barrier and has no analgesic properties and no potential for addiction

**Adverse effects:**

Abdominal pain and distention, constipation, dry mouth, hypersensitivity, and nausea and vomiting.
Adsorbents

1. Kaolin and Pectin:
Kaolin (hydrated magnesium aluminum silicate), often combined with pectin (indigestible carbohydrate).

Mechanism of action:
Adsorb bacterial toxins and fluid

Indications:
Acute diarrhea (given after each loose bowel movement)

Adverse effects:
Not absorbed and has no adverse effects.
2. **Bismuth subsalicylate**: Insoluble complex of bismuth and salicylate

**Mechanism of action:**
- **Bismuth:** antimicrobial
- **Salicylate:** antisecretory

**Adverse effects:** blackening of tongue and stools
Octreotide (somatostatin analogue)

Mechanism of the anti-diarrheal action:

1. It inhibits the secretion of many GIT hormones, including gastrin, cholecystokinin, glucagon, insulin, secretin, pancreatic polypeptide, vasoactive intestinal peptide, and 5-HT3.

2. It reduces intestinal fluid secretion and pancreatic secretion.

3. It slows gastrointestinal motility and inhibits gallbladder contraction.
Indications:

1. Patients with +ve stool culture
2. Patients presented with dysentery
3. Patients with suspected exposure to bacterial infection → Quinolones (as ciprofloxacin)
ANY QUESTIONS...???
THANKS!

Thanks for your attention