

Medical Pharmacology



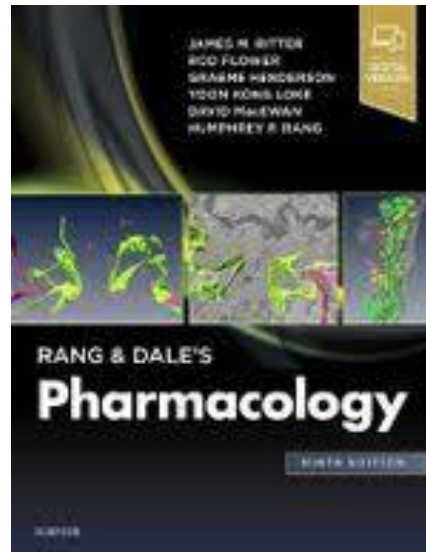
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Celebrating
50
YEARS
1970 - 2020

Gastrointestinal Pharmacology

Lecture 4 – management of constipation & diarrhoea



Rang & Dale's
Pharmacology
9th edn 2020
Chaps 31, 33



Rang & Dale's
Pharmacology
10th edn 2023
Chaps 30, 32

COMMONWEALTH OF AUSTRALIA

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Learning Objectives

By the end of this module, students should be able to demonstrate and apply knowledge of:

- Mechanisms of constipation and diarrhoea
- Pharmacology of drugs involved in the treatment of constipation
 1. Bulk forming laxatives
 2. Stimulant laxatives
 3. Osmotic and saline laxatives
 4. Stool softeners
- Pharmacology of drugs involved in the treatment of diarrhoea
 1. Oral rehydration
 2. Opioid agonists

Constipation

Definition

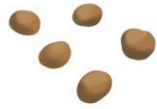
- < 3 times per week (“normal” varies from 2-3 times per day to 2-3 times per week)
- Straining and feeling of incomplete evacuation
- Sensation of anorectal obstruction
- Hard or lumpy stools
- Require the use of other means to facilitate defecation
- Bristol Stool type 1 and 2

Causes

- Neurogenic (neuropathy, spinal cord injury)
- Non-neurogenic (hypothyroidism, hypercalcaemia)
- Irritable bowel syndrome (IBS)
- Drug-induced (antacids, opioids, antimuscarinics, TCAs, iron supplements, muscle relaxants...)
- Stress
- Diet (adults, children)

Bristol Stool Chart

Type 1



Separate hard lumps, like nuts. Hard to pass

Type 2



Sausage-shaped but lumpy

Type 3



Like sausage but with cracks on the surface

Type 4



Like sausage or snake, smooth and soft

Type 5



Soft blobs with clear-cut edges. Passed easily

Type 6



Fluffy pieces with ragged edges, a mushy stool

Type 7



Watery, no solid pieces. Entirely liquid.

Management of Constipation

Diet and lifestyle measures

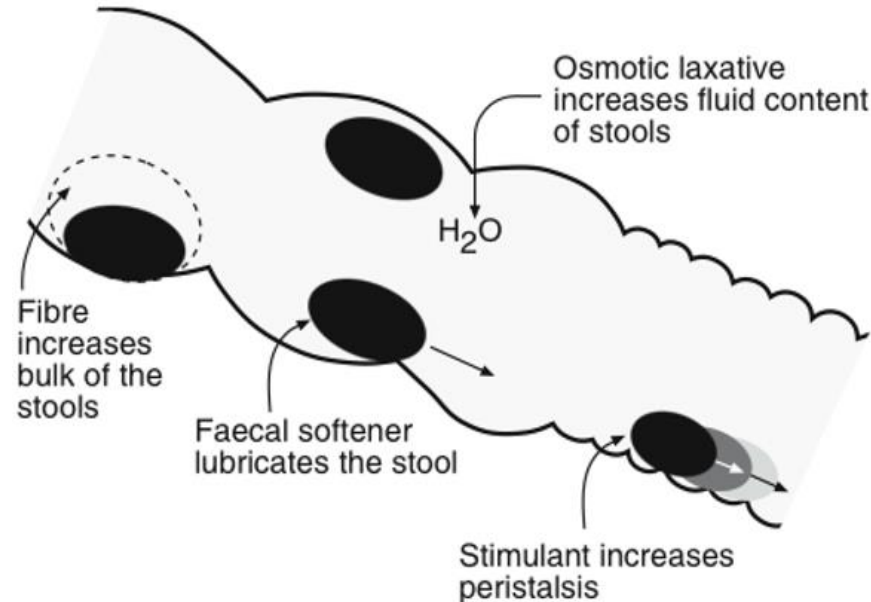
- Adequate dietary fibre intake
- Adequate fluid intake
- Increasing activity/exercise
- Responding to urge to defecate

Laxatives

1. Bulk forming - psyllium husk and bran
2. Stimulant - senna and bisacodyl
3. Osmotic and saline laxatives- lactulose, macrogol, salts
4. Stool softeners - docusate and poloxamer

Laxative Indications

- used to treat constipation, including side effects of opioids
- bowel prep, rectal surgery, perianal disease



1. Bulk-forming laxatives:

- Examples include psyllium husk and bran.
- Absorb water and provide a bulky, hydrated mass in the gut lumen promoting peristalsis and improved faecal consistency.
- Not broken down by the normal digestive process.
- Need to be administered with sufficient fluid.



2. Stimulant Laxatives:

- Examples include senna and bisacodyl.
- proposed actions include decreased aquaporin expression, activation of myenteric motility neurons and submucosal secretomotor neurons
- Promote accumulation of water and electrolytes and stimulate nerve endings to increase intestinal motility.
- Primary effect on small and large intestines- cause cramping/abdominal discomfort
- **minimal adverse effects (diarrhoea); urine discolouration, monitor in hypokalemia**



3. Osmotic and Saline Laxatives:

- Examples: lactulose, macrogol (Movicol), polyethylene glycols (PEGs), glycerol, sorbitol, mannitol and saline laxatives.
- Osmotic laxatives produce an osmotic load (hyperosmotic) and increase the volume of fluid in the lumen, accelerating the transfer of gut contents, resulting in peristalsis and defecation.
- Saline laxatives (eg Epsom salts, magnesium or sodium salts) increase salt in the colon leading to water retention and increased water content in the faeces by osmosis.
- Can cause electrolyte disturbances.
- A rectal preparation in this class is glycerol suppositories (osmotic, lubricant effects and local irritation to promote peristalsis)
- Include oral powders for bowel evacuation prior to gastrointestinal procedures eg: Glycoprep-C, Colonlytely

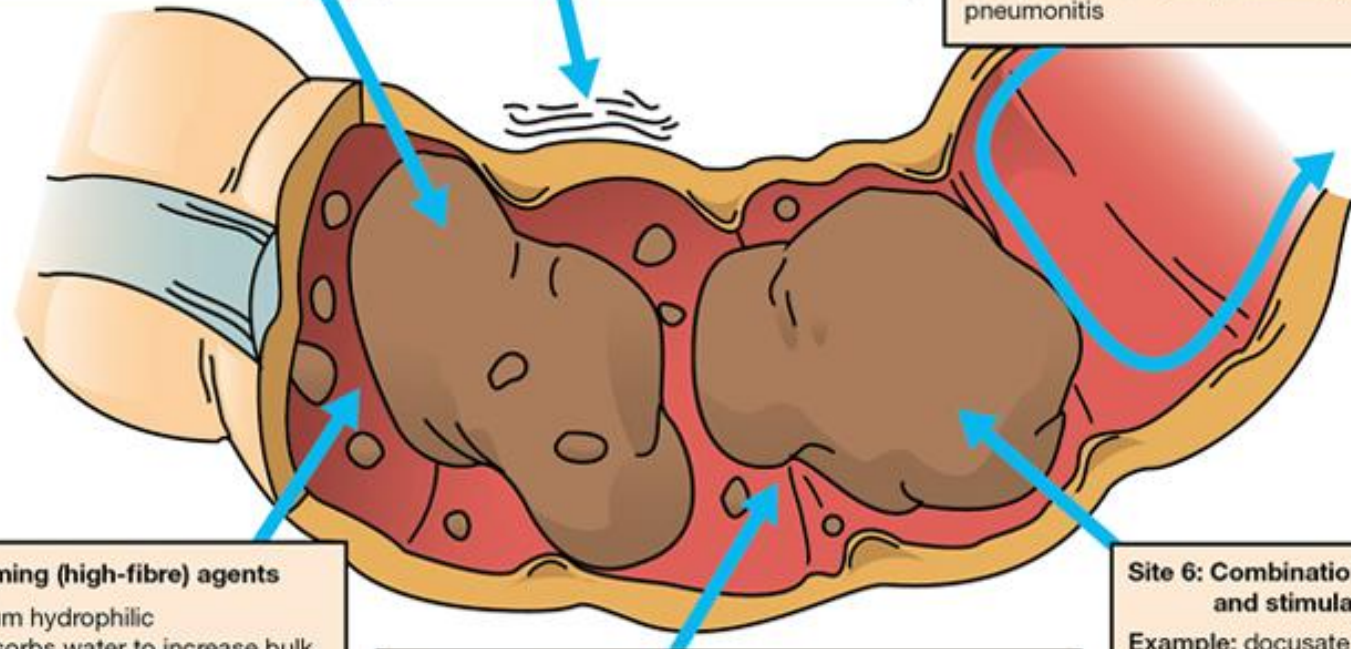
4. Stool Softeners:

- Examples include docusate and poloxamer.
- Surface active compounds that act in the GIT.
- Facilitate the mixing of water and fatty substances in the faecal mass.
- Wetting agents to produce softer faeces.

Site 1: Faecal softeners
Example: docusate
Mechanism: wetting agent used to soften faecal matter
Onset of action: 1–3 days
Comments: Liquid dosage form may cause throat irritation; dilute in fruit juice or milk before administering

Site 3: Stimulants
Example: senna
Mechanism: increases peristalsis via nerve stimulation in the colon
Onset of action: 6–12 hours
Comments: May cause discolouration of faeces and urine (alkaline urine from pink, red to brown; acid urine from yellow to brown)

Site 5: Lubricants/faecal softeners
Example: liquid paraffin
Mechanism: coats surface of faeces and eases passage of stool; also softens faecal mass
Onset of action: 6–8 hours
Precaution: Avoid administering within 2 hours of meals, as it may impair absorption of vitamins A, D, E and K. Avoid use in dysphagic and bedridden persons as aspiration of liquid paraffin may result in lipid pneumonitis



Site 2: Bulk forming (high-fibre) agents
Example: psyllium hydrophilic
Mechanism: absorbs water to increase bulk, distending bowel to initiate reflex bowel activity
Onset of action: 12 hours to 3 days
Comments: Contraindicated in persons with dysphagia, as oesophageal obstruction may result. Avoid in dehydrated persons or individuals with limited or restricted fluid intake

Site 4: Osmotics
Example: lactulose
Mechanism: increases volume of fluid in lumen, resulting in distension, peristalsis and evacuation
Onset of action: 1–3 hours
Comments: Avoid use in colostomy and ileostomy, and in persons with impaired renal function or dehydration

Site 6: Combination of stool softener and stimulant
Example: docusate and senna
Mechanism: stool softener and stimulant
Onset of action: 6–12 hours
Precaution: As noted for individual laxatives

Table – Onset of effect of laxative classes

Class and time to effect	
bulk-forming laxatives	
<i>oral</i> : 2–3 days	
osmotic laxatives	
glycerol, lactulose, sorbitol	<i>oral</i> : 1–3 days; <i>rectal</i> : 5–30 minutes
macrogol	<i>oral</i> : 0.5–3 hours for bowel preparation; 1–3 days for constipation
saline	<i>oral</i> : 0.5–3 hours; <i>rectal</i> : 2–30 minutes
stool softeners	
<i>oral</i> : 1–3 days	
stimulant laxatives	
<i>oral</i> : 6–12 hours; <i>rectal</i> : 5–60 minutes	

Diarrhoea

Definition

- Increased passage of semi-liquid or liquid stools.
- Passage of 3 or more loose stools per day or more frequent than normal for the individual
- Bristol Stool type 6 and 7 are most consistent with diarrhoea

Causes

- Infections (bacterial, viral, parasites etc)
- Drugs (NSAIDs, magnesium, cytotoxic agents, antibiotics)
- Food (poisoning or intolerances)
- Post-surgical issues
- Inflammation in the GIT
- Psychological factors (eg anxiety)

Mechanisms of Diarrhoea

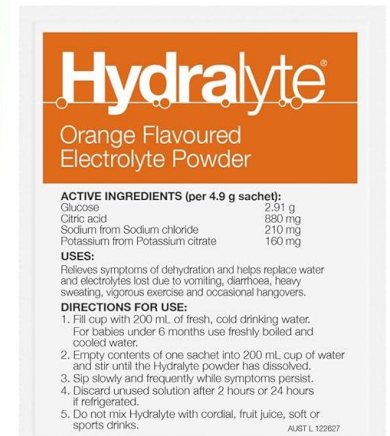
Diarrhoea may be due to decreased absorption by the small and large intestine, accumulation of non-resorbable solutes or excessive secretion in the small intestine and colon.

- Malabsorption/Decreased absorption time- may be due to resection of the small or large intestine
- Osmotic- water retention in the bowel due to the presence of unabsorbable material
- Secretory- more secretion of water and electrolytes into the bowel than is absorbed
- Inflammatory- inflammation or ulceration of the mucosal layer due to disease (may be blood, plasma etc in the faeces)
- Drug induced- drugs or toxins causing stomach upset and diarrhoea

Management of Diarrhoea

Oral rehydration

- First line treatment
- Fluid and salt replacement are essential
- Isotonic solutions of NaCl plus glucose
- Glucose enhances Na reabsorption and water uptake.
- Numerous preparations available
- IV rehydration in some circumstances



Other treatments

- Antimicrobials to treat the infection responsible for the diarrhoea

Management of Diarrhoea - Opioid Antidiarrhoeals

Opioid agonists slow GI motility by activating mu opioid receptors on intestinal smooth muscles, resulting in a reduction in secretions and inhibition of propulsive movements in the gut.

Loperamide

- Agent of choice
- agonists at μ -opioid receptors **on enteric nerves**
- stimulate presynaptic inhibition of release of ACh and other ENS transmitters, reducing propulsive peristalsis & increasing fluid absorption
- Has a relatively selective action on the GIT
- Affects intestinal motility, has antisecretory effects, decreases the passage of faeces
- Adverse effects: abdominal pain, bloating, constipation
- Is more potent than morphine but does not cross the BBB, therefore no CNS effects.



Diphenoxylate

- Also lacks morphine-like activity in the CNS but large doses produce typical opioid-like effects.
- Is available as an S3 product in combination with atropine (a muscarinic antagonist)
- The role of atropine is to limit drug diversion (causes dry mouth, blurred vision, urinary retention)