PHARMACOLOGY

TEAM 432

Drugs used in treating constipation and IBS

Objectives

Were not provided.

Color Guide

Slides = Black
Females slides = Green
Males slides= Blue
Explanation=Orange

This lecture was done by:
Ibrahim alqasir / Hossam alshehri

And was reviewed by:
Latifah Al-Fahad

General information

What is constipation?

infrequent defecation, often with straining and the passage of hard, uncomfortable stools.

May be accompanied by other symptoms:

- **Abdominal and rectal pain**
- **Flatulence**
- **Loss of appetite**
- **Lethargy**
- **Depression**

Causes of constipations

Decreased motility in colon:

Decrease in water and fiber contents of diet.

Difficulty in evacuation:

Local painful conditions: Anal fissures, piles

Lack of muscular exercise

Drug-induced:

Anticholinergic agents

Opioids

Antipsychotics

Iron

Treatment of Constipation

General Measures :

1. **Adequate fluid intake.**
2. **High fiber contents in diet.(non absorbable>> increase GI motility**
3. **Regular exercise**
4. **Regulation of bowel habit.**
5. **Avoid drugs causing constipation.**
6. **Use drugs (laxatives or purgatives)**

Medications used in constipations

Drugs that hasten the transit of food through the gastrointestinal tract are called laxatives or purgatives.

Classification of laxatives:

Bulk forming laxatives

Osmotic laxatives

Stimulant laxatives

Stool softeners (lubricants)

Bulk (fiber) Laxatives

Increase volume of non-absorbable solid residue

	Mechanism of Action	Side Effects
Dietary fibers: -Indigestible parts of vegetables & fruits -Bran powder Hydrophilic colloids: -Psyllium seed -Methyl cellulose -Carboxymethyl cellulose (CMC)	Dietary fibers and hydrophilic colloids are non absorbable substances → Increase the bulk of intestinal contents by water retention → ↑mechanical pressure on the walls of intestine >> stimulation of stretch receptors → ↑peristalsis → evacuation of soft stool.	-Delayed onset of action (1-3 days).till defecation happens ,given in chronic not acute conditions -Intestinal obstruction (should be taken with enough water). -Bloating, flatulence, distension -Interfere with other drug absorption e.g. iron, cardiac glycosides. (separate time of administration)

The have high molecular weight so they're not absorbed ➔ drag water into intestinal lumen.

Osmotic Laxatives

Increase water content in large intestine.

-are water soluble compounds

-Poorly absorbable compounds (salts or sugars) 95% non abosrbed, 5% abosrbed

-They remain in the bowel, attract and retain water by osmosis thereby increasing the volume of feces → ↑ peristalsis → evacuation of stool.

Include:	Info/MOA	USES	Side effects
Sugars e.g. lactulose **Dose:15 ml for constipation and 30 for liver cirrhosis**	-Semisynthetic disaccharide of fructose & galactose. -Non absorbable (no enzymes to degrade it) -In colon, metabolized by bacteria into fructose and galactose (monosaccaridess(-These sugars are fermented into lactic acid and acetic acid that function as osmotic laxatives	-Prevention of chronic constipation -Hepatic encephalopathy (Hyperammonemia) -Hemorrhoids	-Delayed onset of action (2-3 days) -Abdominal cramps and flatulence (accumulation of gasses cuz it's not absorbable). -Electrolyte disturbances.

❖Lactulose increases the H^+ concentration in the gut, This favors the formation of the non-absorbable NH_4^+ from NH_3, trapping NH_3 in the colon and reducing its back diffusion into blood.

❖Why Lactulose is commonly used in liver cirrhosis?

It's degraded into Lactic acid + Acetic Acid that lower the pH of the colon ➔ ↓ ammonia absorption

These acids are the ones responsible for osmosis (they're doing all the work)

Osmotic Laxatives (Cont.) Increase water content in large intestine.

Include:	Info/MOA	USES	Side effects
Salts (Saline laxatives) **e.g.** **1.Magnesium sulphate or hydroxide.** **2. Sodium or potassium phosphate.**	-Are poorly absorbable salts -Increase evacuation of watery stool. -Magnesium sulphate (Epson's salt). -Magnesium hydroxide (milk of magnesia). -Sodium phosphate or potassium phosphate. -have rapid effect (within 1-3 h). -Isotonic or hypotonic solution should be used. Na salts>> cardiac arrhythmia M sulfate>>antiacid, treats constipation>>cause diarrhea	Treatment of *acute* constipation Ex: taking aminoglycoside or myasthenia gravis	-Disturbance of fluid and electrolyte balance (volume depletion) -May have systemic effects.(5% absorbed) **Contraindications:** 1.Sodium salts in CHF 2.Magnesium salts in: -Renal failure -Heart block -CNS depression -Neuromuscular block
Polyethylene glycol (PEG) **No osmotic activity**	-Isotonic solution of polyethylene glycol & electrolytes (NaCl, KCl, Na bicarbonate). -Is a colonic lavage solution **Advantages:** •Limited fluid or electrolyte imbalance •less flatulence and cramps	Used for whole bowel irrigation prior to colonoscopy or surgery (4L over 2-4 hours).	These are caused by the small absorbed amounts of Na and Mg salts.

Stimulant Laxatives

Act by direct stimulation of nerve endings in colonic mucosa (ENS).

- **are the most powerful group among laxatives and should be used with care.**

Mechanism of Action:

act via direct stimulation of enteric nervous system ➔ increased peristalsis & purgation.

Include	info	contraindications
Bisacodyl	Is given orally, acts on colon Onset of action = orally (6-12 h)/ per rectum (1h) Dihenylmethane derivative	----
Castor Oil	-Given orally -5-20 ml on empty stomach in the morning. -acts in small intestine -Vegetable oil degraded by lipase→ ricinoleic acid + glycerin -Ricinoleic acid is very irritating to mucosa. Onset of action = 2-6 h.	Castor oil in pregnancy → reflex contraction of uterus → abortion.

These drugs are slower than the osmotic laxatives.

Stimulant Laxatives (Cont.)

Act by direct stimulation of nerve endings in colonic mucosa (ENS).

Include	info	contraindications
Anthraquinone glycosides **senna, cascara, aloe vera**	-Act in colon -Hydrolyzed by bacterial colon into sugar+ emodin (The absorbed emodin has direct stimulant action). -Emodin may pass into milk. -Delayed onset of action (8-12 h). -Bowel movements in 12 h (orally) or 2 h (rectally). -Given at night.	Senna is contraindicated in lactation

Side effects of this group:

-Abdominal cramps may occur.

-Prolonged use → dependence & destruction of myenteric plexus leading to atonic colon.

(Fecal Softeners (Lubricants /surfactants

Alter the consistency of feces → easier to pass

-Are non absorbed drugs

-Act by either decreasing surface tension or by softening the feces thus promoting defecation.

-Treat constipation in patients with hard stool or specific conditions and for people who should avoid straining (hospitalized or post surgical patients)

Include	
Docusate	-Sodium dioctyl sulfosuccinate -One type of surfactants -Act by decreasing surface tension of feces (allow H2O penetration into feces>>decrease consistency) -is given orally (1-3 days) or enema (5-20 min).
Paraffin oil	-Is a mineral oil, is given orally and acts as lubricant thus softening the feces and promoting defecation. -Good for radiology preparation but not palatable -impairs absorption of fat soluble vitamins.
Glycerin	Lubricant Given rectally (suppository)

Because fat-soluble vit. dissolve in this oil and get eliminated in the stool.

Irritable bowel syndrome (IBS)

Chronic bowel disorder characterized by abdominal discomfort (bloating, pain, distention, cramps) associated with alteration in bowel habits (diarrhea or constipation or both). (TREAT SYMPTOMs)

Symptomatic Treatment	
Antispasmodics e.g. mebeverine (for the cramps),can be treated by smooth muscle relaxant such as anticholinergic drugs)	
Low doses of tricyclic antidepressants (amitriptyline). Act by: •Anticholinergic action •Reduce visceral afferent sensation	
Laxatives in IBS-Constipation	e.g. Tegaserod
Antidiarrheals in IBS-Diarrhea	e.g. Alosetron

Discussed in the next slide

Irritable bowel syndrome (IBS)

Alosetron (IBS-Diarrhea)	▪Selective $5HT_3$ antagonist (taken as antiemetic) ▪block 5-HT_3 receptors of the enteric nervous system of the gastrointestinal tract ▪inhibition of colon motility. ▪inhibition of unpleasant visceral afferent pain sensation (nausea, pain, bloating).	**Indication:** severe IBS with diarrhea in women **Side Effects:** Constipation and ischemic colitis
Tegaserod (IBS-Constipation)	▪$5HT_4$ agonist. Has prokinetic effect>> increase GI motility >> treat constipation ▪Stimulation of $5HT_4$ of enteric nervous system of GIT ➔ increases peristalsis	**Indication:** Short term treatment of IBS-associated with constipation in women. ➢Restricted to special patients that require hospitalization

Summary

Bulking agents	Oral, 48–72 hours	acute & chronic constipation
stool softeners	oral, 24–72 hours; rectal, 5 --20 minutes	prevention of straining after rectal surgery and in acute perianal disease
Osmotic laxatives (lactulose)	oral, 24–72 hours	- chronic constipation -hepatic encephalopathy - opioid constipation
Saline laxatives	oral, 0.5–3 hours; rectal, 30 minutes	short term treatment of moderate-to-severe constipation; chronic constipation; bowel preparation

Summary from 431 team

Drug	MOA	Uses	Pharmacokinetics	ADRs
1-Bulk purgatives 1. Dietary fibers: undigested polysaccharide vegetables, fruits, grains, bran, pectin. 2. Natural plant products &semi synthetic hydrophilic colloids (very important): -Psyllium seed, methyl cellulose -Carboxymethyl cellulose (CMC). 3. Synthetic non absorbed resins: Calcium polycarbophil	Non-absorbed hydrophilic colloids → Increase the bulk of intestinal contents by water absorption → ↑ mechanical pressure on the walls of intestine → stimulation of stretch receptors → ↑ peristalsis.	-Hemorrhoids; Pregnancy; Colostomy; ileostomy; anal fissure; IBS, UC, -Chronic diarrheas with diverticular disease. (a disease characterized by outpocketings of the colonic mucosa and submucosa through weaknesses of muscle layers in the colon wall.)		-Delayed onset of action (several days 1-3). -Intestinal obstruction -Malabsorption syndrome, abdominal distention. -Interfere with other drug absorption e.g. iron, calcium, and cardiac glycoside (digoxin). So we should separate the drug in time
2- Osmotic Purgatives Water Soluble but non absorbable compounds ,Increase water content in large intestine				
A) Organic (Sugars): lactulose (semisynthetic disaccharide of fructose and galactose).	-Metabolized by colonic bacteria into fructose and galactose. -These sugars are fermented into lactic acid and acetic acid that function as osmotic laxatives.	• Prevention of chronic constipation • Treatment of hepatic encephalopathy	• Delayed onset of action (2-3 days)	• Abdominal cramps and flatulence. • Electrolyte disturbance.(Because of the water drainage)
B) Non-organic (Saline purgatives): Magnesium salts, sodium or potassium salts Contraindicated : -Elderly patients -Renal insufficiency. -Sodium salts: in CHF -Magnesium salts : renal failure, heart block, CNS depression, neuromuscular block	Are poorly absorbed salts. They remain in the bowel and retain water by osmosis thereby increasing the volume of feces → ↑ distension → ↑ peristalsis → evacuation of watery stool.	• Treatment of acute constipation because it has rapid action • Prevention of chronic constipation	• Rapid effect (within 1-3h). • Isotonic or hypotonic solution should be used	1. Intravascular volume depletion. 2. Electrolyte fluctuations: severe in children 3. May have systemic effect

Balanced polyethylene glycol (PEG*)

- Balanced isotonic solution of osmotically active sugar, NaCl, KCl, Na bicarbonate
- No intravascular fluids or electrolyte shifts
- No flatus or cramps
- Lavage solution
- Used for complete cleansing prior to gastrointestinal endoscopic procedures (4L over 2-4 hours)
- small doses used for treatment or prevention of chronic constipation

3 - Stimulant Purgatives (cathartics) act via direct stimulation of enteric nervous system → peristalsis & purgation and it's ADRs are: 1-Abdominal cramps may occur 2-Prolonged use → dependence & destruction of myenteric plexus and atonic colon.			
a. Bisacodyl.	-Acts on large intestine (weak).	-Onset time 6-10 h, taken at night.	
b. Anthraquinone derivatives. Senna, Cascara, Aloes	-In colon, glycosides are hydrolyzed by bacteria into emodin + sugar -The absorbed emodin has direct stimulant action on myenteric plexus → ↑ smooth muscle contraction → defecation.	-Bowel movements in 12 h (orally) or 2 h (rectally). -Given at night. -Emodin may pass into milk	-Causes brown pigmentation of the colon (melanosis coli). Senna is contraindicated in : Lactation
c. Castor oil. -Fixed oil degraded by lipase in upper small intestine → ricinoleic acid + glycerin -Ricinoleic acid irritates mucosa. Acts on small intestine (strong). -5-20 ml on empty stomach in the morning. -O.T. = 4 h.			Contraindicated in : Pregnancy → abortion
4 - Fecal Softeners (Lubricants) • Are non absorbed drugs that soften the feces ,thus promoting defecation. • May be given orally or rectally(faster).			
A)Surfactants e.g. Docusate (sodium dioctyl sulfosuccinate).	decrease surface tension of feces	Is commonly prescribed in hospitalized patients to minimize straining.	• is given orally or enema.
B)Glycerin (Suppository)		(Usually given twice after surgery to avoid any damage to the Surgery) and it's preferable with children	
C)Mineral oil (Liquid Paraffin)		(Good for radiology preparation) given in enema in that case.	• Not palatable (bad taste) • Impairs absorption of fat soluble vitamins. • Increase activity of oral anticoagulant.

Treatment of IBS

- Antispasmodics e.g. mebeverine (atropine like action)
- Low doses of tricyclic antidepressants (amitriptyline) : * Anticholinergic action * reduce visceral afferent sensation
- Alosetron (diarrhea)
- Tegaserod (constipation)

	Alosetron	Tegaserod
MOA	5-HT3 receptor antagonists	5-HT4 partial agonist
USES	Woman with IBS and sever diarrhea	Woman with IBS and constipation
Side effects	Constipation; Ischemic Colitis	Diarrhea; Headache

MCQs

1/ Patient complaining of constipation, was treated… few days later he came to the ER with Obstruction in his bowl which one of the following could be the reason:

a) Bulk Laxatives

b) Osmotic Laxatives

c) Stimulant Laxatives

2/ IBS with Diarrhea use which one of the following:

a) Alosetron

b) Tegaserod

c) amitriptyline

1/a 2/a

PHARMACOLOGY

TEAM 432

Pharmacology leaders:
Tuqa Alkaff & Abullah Alanzi

Email:
Pharmacologyteam1@gmail.com