DRUGS FOR CONSTIPATION AND DIARRHEA

By

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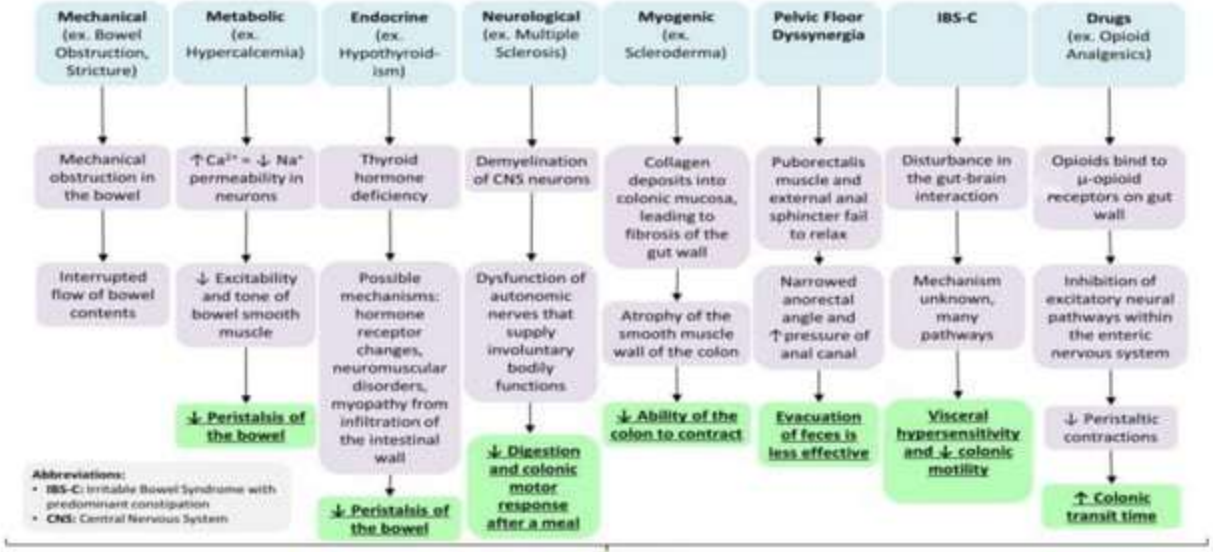
Pathogenesis of Select Causes of Constipation in Adults and in Elderly



CONSTIPATION

Common complaint in clinical practice.

Definition of constipation includes the following:

- Infrequent bowel movements (typically three times or fewer per week)
- Difficulty during defecation
- The sensation of incomplete bowel evacuation.
- Rome III criteria are widely used to diagnose chronic constipation.

CONSTIPATION

DIAGNOSTIC CRITERIA OF CONSTIPATION - 2 or more of criteria listed below:

- Straining efforts in course of defecation at least in 25% of defecations
- Solid stool at least in 25% of defecations
- Feeling of incomplete evacuation at least in 25% of defecations
- Feeling of anorectal obstruction at least in 25% of defecations
- Need in hand manipulation to facilitate the defecation at least in 25% of defecations
- Less than 3 defecations per week.

Criteria fulfilled for the last 3 months with symptom onset.

MANAGEMENT DRUGS FOR CONSTIPATION - CLASSIFICATION

BULK FORMING:-

Dietary fiber : Bran, psyllium, ispaghula, methylcellulose

STOOL SOFTENER:-

Docusates(DOSS),
Liquid paraffin

STIMULANT PURGATIVES:-

- Diphenylmethane- Phenolphthalein, Bisacodyl, sodium picosulfate
- Anthraquinones (emodins)- senna
- 5-HT4 agonist- Prucalopride
- Castor oil.

OSMOTIC PURGATIVES:-

- Magnesium salts: suflate, hydroxide
- Sodium salts: sulfate, phosphate
- Sod.pot.tartrate
- lactulose

BULK FORMING LAXATIVES

Dietary fibre bran :

Residual product of flour industry which consist of 40% of dietary fiber.

Consist of un-absorbable – cellulose , lignin, pectins, glycoprotiens & other polysaccharides.

Mechanism of action:-

Absorbs water in the intestines, swells, increases water content of faces- softens it and facilitates colonic transit.

Dietary fiber supports bacterial growth in colon which contribute to fecal mass.

PSYLLIUM & ISPAGHULA

They contain natural colloidal mucilage

Mechanism of action:

Forms a gelatinous mass by absorbing by water

Largely fermented in colon increase bacterial mass & softens the faeces.

Uses: Useful in both constipation & diarrhoea

Drawbacks:

If taken dry ,can cause esophageal impaction

Dose: 3-12 g refined husk freshly mixed with water or milk and taken daily –acts in 1-3 days.

STOOL SOFTNER

DOCUSATES (DIOCETYL SODIUM SULFOSUCCINATE:DOSS)

It is a anionic detergent, softens the stool by decreasing the surface tension of fluids in bowel.

Emulsifies the colonic content and increases penetration of water into the faeces.

Dose: 100-400 mg/day

Uses: Indicated when straining at stools must be avoided.

Drawback: Can disrupt the mucosal barrier and enhance absorption of many non-absorbable drugs eg liquid- paraffin –should not be combined with it

Cramps and abdominal pain can occur.

Bitter; liquid preparation may cause nausea

LIQUID PARAFFIN

It is a viscous liquid

A mixture of petroleum hydrocarbon

Uses - Soften stools and is said to lubricate by coating them

Dose 15-30ml/day-oil as such or in emulsified form

Drawback Unpleasant to swallow

Small amount passes into intestinal mucosa →may produce foreign body granuloma in intestinal submucosa.

Carries away fat soluble vitamins with it into the stools; deficiency may occur on chronic use

STIMULANT PURGATIVES

DIPHENYLMETHANES: Phenolphthalein, Bisacodyl

Activated in intestine by deactylation

Site of action is in **colon**: irritate the mucosa, produce mild inflammation → stimulate peristalsis.

Dose: Phenolphthalein: 60-130 mg Bisacodyl: 5-15 mg

Drawback: Allergic reaction- skin rashes, fixed drug eruption ,Stevens-Johnson syndrome have been reported.

Phenolphthalein has been found to produce tumours in mice and genetic damage; the US-FDA has ordered its withdrawal from market.

ANTHRAQUINONES

Senna is obtained from leaves of certain Cassia sp.

Cascara, sagrada is the powdered bark of the buck-thorn tree.

These contain anthraquinone -glycosides ,also called Emodins.

Mechanism of action:- In the colon bacteria liberate the active anthrol form, which either acts locally or is absorbed into circulation. The active principle acts on the myenteric plexus to increase peristalsis.

Dose: 12- 18 mg

Drawback: Skin rashes are seen occasionally

Regular use for 4-12 months causes mucosal pigmentation (melanosis).

PRUCALOPRIDE

It is a selective 5-HT4 receptor agonist marketed recently in UK, Europe and Canada for chronic constipation, when other laxative fail.

It activates 5-HT4 receptor on intrinsic enteric neurons to promoting propulsive contraction in ileum and more prominently in colon

Enhance release of excitatory transmitter Ach

Colonic transit and stool frequency is improved - predominant irritable bowel syndrome.

Dose:- 2 mg OD.

Side effect:- Headache, dizziness, fatigue, abdominal pain & diarrhea.

CASTOR OIL

Bland vegetable oil ⇒ the seeds of *Ricinus communis*

Mechanism of action: It mainly contain triglyceride of ricinoleic acid which is a polar long chain fatty acid.

Castor oil hydrolysed in the ileum by lipase to ricinoleic acid.

Which acts primarily in the small intestine to stimulate secretion of fluid and electrolytes and speed intestinal transit.

Dose: 30 ml oil

Drawbacks: Unpalatable, Frequent cramping, possibility of dehydration and after constipation (due to complete evacuation of colon).

OSMOTIC PURGATIVE

Solute that are not absorbed in the intestine retain water osmotically and distend the bowel –increasing peristalsis indirectly.

Magnesium salt also release cholecystokinin which augment motility and secretion.

Dose: Mag.hydroxide (as 8% w/w suspension-milk of magnesia) 30ml.

Mag.sulfate : 5-15g.

Sod.sulfate : 10-15g.

Sod.phosphate: 6-12g

Sod.pot.tartrate: 8-15g

Salt taken in above mentioned doses, dissolved in 150-200 ml of water

Drawback: Unpleasant, vomiting, produce watery stool & after constipation

LACTULOSE

It is a disaccharide of fructose and lactose which is neither digested nor absorbed in the small intestine-retains water.

It increase fecal bulk by hydrophilic action and also due to osmotic action.

Dose: 10 mg BD with plenty of water

Drawback: Flatulence and flatus is common, cramp also occur. Nausea due to its peculiar sweet taste.

LAXATIVES				
DRUG NAME	**magnesium hydroxide, magnesium citrate, sodium phosphate, lactulose, polyethylene glycol**	**methylcellulose, polycarbophil, psyllium**	**bisacodyl, senna**	**docusate**
CLASS	Osmotic laxatives	Bulk-forming agents	Stimulant laxatives	Stool softeners
MECHANISM OF ACTION	Draw water into the lumen to increase intestinal peristalsis	Draw water in the stool, forming a soft, bulky mass, which stimulates intestinal peristalsis	Irritate nerve endings in the intestinal walls, stimulating smooth muscle contraction and intestinal peristalsis	Act as surfactant that allows the water to penetrate the stool and make it softer
INDICATIONS	Constipation			
ROA	PO, REC			
SIDE EFFECTS	Diarrhea, Fluid loss Lactulose - Cramping, Bloating, Flatulence	Nausea, Vomiting, Bloating, Flatulence, Diarrhea	Abdominal cramping, Nausea, Vomiting, Diarrhea, Weakness, Fluid and electrolyte imbalance **Senna** - Reddish brown urine, Melanosis coli	Nausea, Vomiting, Abdominal cramping, Diarrhea
CONTRA-INDICATIONS AND CAUTIONS	•Intestinal obstruction •Severe abdominal pain •Symptoms of appendicitis, diverticulitis, ulcerative colitis For saline laxatives: Renal, hepatic impairment, Cardiac conditions For lactulose: Diabetes mellitus			

LAXATIVES	
ASSESSMENT AND MONITORING	•**All laxatives** Client history: normal elimination pattern, medications or conditions that may contribute to constipation •Current symptoms; onset and duration; stool characteristics and frequency; presence of flatus, abdominal pain, nausea, straining •Abdominal assessment •Vital signs, Laboratory results: CBC, comprehensive metabolic panel, thyroid function tests •Therapeutic effect: relief of symptoms and return to normal elimination pattern
CLIENT EDUCATION	Take as directed with at least eight ounces of water - Increase daily fluid intake •Prolonged use of laxatives can cause dependence •Contact the health care provider: • if constipation is unrelieved • signs or symptoms of dehydration or electrolyte imbalance •Lifestyle modifications • Increase fiber-containing food, physical activity, and fluids • Do not ignore urge to defecate **Osmotic laxatives -** Follow each dose by eight ounces of water **Bulk-forming agents** Powder: take with a full eight ounce glass of water or juice, drink right right after mixing, immediately follow with an additional eight ounces of water •Separate fiber laxative and other medications by 1–2 hours **Stimulant laxatives -** Temporary discoloration in urine **Emollient laxatives (stool softeners) -** May take up to three days for results

ANTI-DIARRHOEAL AGENTS

DIARRHOEA

It is defined by WHO as 3 or more loose or watery stool in a 24-hour period.

Diarrheal diseases constitute a major cause of morbidity and mortality worldwide; especially in developing counties.

Global burden of pediatric diarrhoea is estimated to be 1.5 billion episodes with 1.5-2.5 million deaths under 5 year of age per year.

In India around 1000 children die every day due to diarrhea.

Main cause of death from acute diarrhoea is dehydration.

Other important causes of death are dysentery and under-nutrition.

Types of Diarrhoea

Acute Diarrhoea:

Sudden onset and lasts less than two weeks

90% are infectious in etiology

Chronic Diarrhoea:

Diarrhoea which lasts for more than 4 weeks

Most of the causes are non-infectious

Persistent Diarrhoea:

Diarrhoea lasting between 2 to 4 weeks

MANAGEMENT

Diarrhoea therapeutic measures may be grouped into:

A) Treatment of fluid depletion, shock and acidosis.

B) Maintenance of nutrition.

C) Drug therapy.

Treatment of fluid depletion, shock & acidosis

Rehydration:

Done by (i) intravenous (ii) oral Intravenous rehydration:

It is needed only when fluid loss is severe i.e., > 10% body weight,

If patient is losing > 10 ml/kg/hr, unable to take enough oral fluids due to weakness, stupor or vomiting.

The recommended composition of i.v. fluid is:

NaCl = 5g in 1L of water

KCI = 1 g or 5% glucose

NaHCO3 = 4 g solution.

Volume equivalent to 10% BW should be infused over 24 hours; the subsequent rate of infusion is matched with the rate of fluid loss.

ADMINISTRATION OF ORT

Patients are encouraged to drink ORS at ½-1 L hourly intervals.

Initially 5-7.5% BW volume equivalent is given in 24 hours (5 ml/kg/hr in children).

Subsequently it may be left to demand but should at least cover the rate of loss in stools.

ZINC IN PEDIATRIC DIARRHOEA

WHO have recommended that all children with acute diarrhoea should be given zinc supplementation along with ORS and continued for next 10-14 days.

Zinc supplementation :

10 mg/day for 0-6 month age

20 mg/day for 6-60 month age

With ORS reduce the duration and severity of acute diarrhoea.

Reduce recurrences of diarrhea for next 2-3 month.

MAINTENANCE OF NUTRITION

- Breast milk or ½ strength buffalo milk
- Boiled potato
- Cooked rice
- fruit juices
- chicken soup
- banana
- sago should be given as soon as the patient can eat.

Avoiding fats, high fibre foods and alcohol generally improves patient comfort.

DRUG THERAPY

Drug used in diarrhea can be categorized in to

1. Specific antimicrobial drugs
2. Probiotics
3. Nonspecific anti-diarrhoeal drugs

Antimicrobials are of no value :

- In diarrhoea due to non infective causes.
- Irritable bowel syndrome (IBS)
- Coeliac disease
- Pancreatic enzyme deficiency
- Thyrotoxicosis
- Rotavirus.

ANTIMICROBIAL ARE USEFUL ONLY IN SEVERE DISEASE :TRAVELERS DIARRHOEA:

mostly due to **ETEC, campylobacter**: cotrimoxazole, norfloxacin reduces the duration.

EPEC: is less common, but causes shigella like invasive illness. Cotrimoxazole or norfloxacin may be used in acute cases and in infants

YERSINIA ENTEROCOLITICA: common in colder places, cotrimoxazole is the most suitable drug in severe cases.

SHIGELLA ENTERITIS: only when associated with blood and mucus in stools may be treated with ciprofloxacin or norfloxin.

SALMONELLA TYPHIMURIUM ENTERITIS is often invasive; severe cases may be treated with ciprofloxacin or cotrimoxazole

PROBIOTIC IN DIARRHOEA

These are microbial cell preparation, either live culture or lyophilized powder

Intended to be restore and maintain healthy gut flora.

Diarrheal illnesses and antibiotic use are associated with alteration in the population, composition and balance of gut microflora.

Recolonization of gut by non-pathogenic, mostly lactic acid forming bacteria and yeast is believed to help restore this balance.

Organism most commonly used are

- Lactobacillus sp
- Bifidobacterium sp
- Streptococcus faecalis
- Enterococcus sp.
- yeast
- Saccharomyces boulardii.

NONSPECIFIC ANTIDIARRHOEAL AGENTS

ABSORBANTS: ISPAGHULA , PSYLLIUM, METHYLCELLULOSE
ANTISECERTORY: RECECADOTRIL, BISMUTH SUBSALICYLATE
ANTICHOLINERGICS: OCTREOTIDE
ANTIMOTILITY: CODEINE, DIPHENOXYLATE, LOPERAMIDE

ABSORBANTS

These are colloidal bulk forming substance which absorb water & swell.

They modify the consistency and frequency of stool but do not reduce the water and electrolyte loss.

ispaghula and other bulk forming colloids are useful in both constipation and diarrhea.

ANTISECRETORY DRUGS

RACECADOTRIL: This is a prodrug is rapidly converted to thiorphane ,an enkephalinase inhibitor.

It prevent degradation of endogenous enkephalins(ENKs)

Mechanism of action: Decreases intestinal hypersecretion ,without affecting motility.

Dose: 100mg (children 1.5 mg/kg) TDS for 7 days

Drawback: Nausea, vomiting, drowsiness flatulence.

BISMUTH SUBSALICYLATE

Bismuth is thought to have anti-secretory, anti-inflammatory, and antimicrobial effects.

Mechanism of action:

Stimulation of absorption of fluids and electrolytes by the intestinal wall (antisecretory action)

Reducing inflammation/irritation of stomach through inhibition of prostaglandin

Prevention and treatment of traveller's diarrhea, effective in other episodic diarrhea.

Dose: Taken as suspension 60 ml 6 hourly.

Drawback: Dark stools and black staining of the tongue

OCTREOTIDE

Analog of somatostatin (SST), effective in inhibiting the severe secretory diarrhea associated with hormone-secreting tumors of the pancreas and the GI tract.

Mechanism of action: inhibition of hormone secretion, including 5-HT and various other GI peptides (e.g., gastrin, vasoactive intestinal polypeptide (VIP),secretin, etc.).

Uses: Diarrhoea associated with carcinoid and VIP secreting tumours

Refractory diarrhea in AIDS.

Dose: 50 -100 µg given S.C 2-3 times a day

Drawback: Short-term therapy leads to nausea, bloating, or pain at sites of injection. Long-term therapy can lead to gallstone formation.

OCTREOTIDE

BINDING to SOMATOSTATIN RECEPTORS

↓

INHIBITING HORMONE RELEASE
by PANCREAS & GI TRACT

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SLOWING DOWN PERISTALSIS

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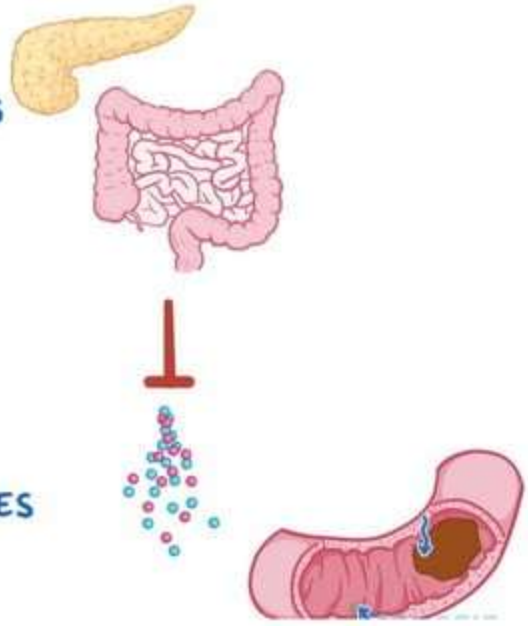
↓↓ SECRETION of FLUID & ELECTROLYTES
into BOWEL LUMEN



ANTIMOTILITY DRUG

These are OPIODS drugs which increase small bowel tone and reduce propulsive movement and diminish intestinal secretion while enhancing absorption.

Major action mediated through μ opioid receptor.

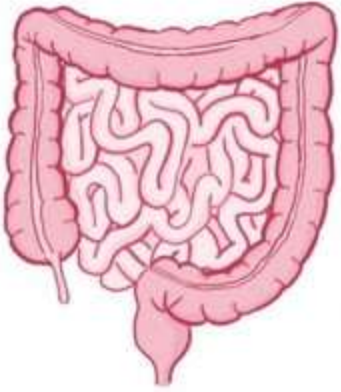
Direct action on intestinal smooth muscle and secretory/ absorptive epithelium also observed.

δ receptor are promote absorption and inhibit secretion.

μ receptor enhance absorption and decrease propulsive movement

OPIOIDS

* TAKEN ORALLY



WORK by **STIMULATING OPIOID RECEPTORS** in INTESTINAL WALL

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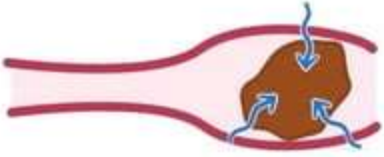
↓↓ PERISTALSIS



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↑↑ **ABSORPTION** of FLUID & ELECTROLYTES into FECAL MASS

DIPHENOXYLATE

Synthetic opioids, used exclusively As anti-diarrheal agents.

Available small doses of atropine to discourage abuse.

Dose: 25 μg atropine sulfate with 2.5 mg diphenoxylate

Two tablets initially, then one tablet every 3-4 hours, not to exceed eight tablets per day.

Drawback: CNS effects - higher doses (40-60 mg per day) and potential for abuse and/or addiction. Respiratory depression, constipation

LOPERAMIDE

Opiate analogue with major peripheral opioids and weak anticholinergic property.

Anti-secretory activity against cholera toxin and some forms of Escherichia coli toxin, Gi-linked receptors countering the increase in cellular cyclic AMP generated in response to the toxins.

Dose: 4mg followed by 2mg after each motion (max 10mg in a day)

2mg BD for chronic Diarrhoea.

Drawback: Abdominal cramps and rashes are most common.

Paralytic ileus, toxic megacolon, abdominal distension in young children. CNS effect are rare.

ANTIDIARRHEALS			
DRUG NAME	**loperamide, diphenoxylate, difenoxin, paregoric**	**octreotide**	**bismuth subsalicylate**
CLASS	Opioid and opioid-related agents	Somatostatin analogue	Adsorbent
MECHANISM OF ACTION	•Decrease intestinal peristalsis	•Inhibits pancreatic and gastrointestinal hormone release •Slows down peristalsis •Decreases secretion of fluid and electrolytes into the bowel lumen	•Protective: Coats the intestinal walls •Antimicrobial: kills causative bacteria •Antisecretory: reduces fluid secretion into the bowel lumen
INDICATIONS	Diarrhea		
ROA	PO	PO, SQ, IM, IV	PO
SIDE EFFECTS	•Constipation •CNS and respiratory depression •**Loperamide:** torsades de pointes and sudden death with high doses (**boxed warning**)	•Constipation •Impaired gallbladder function and cholelithiasis	•Constipation
CONTRA INDICATIONS AND CAUTIONS	•Hepatic or renal impairment •Diarrhea caused by bacteria like *Clostriodiodes*, *Salmonella*, *Shigella*, or *E. coli* For diphenoxylate and difenoxin: Children younger than four and older adults •Narrow angle glaucoma	•Diarrhea caused by bacteria like *Clostriodiodes*, *Salmonella*, *Shigella*, or *E. coli*	•Children recovering from a viral infection •Clients taking aspirin

ANTIDIARRHEALS			
DRUG NAME	**loperamide, diphenoxylate, difenoxin, paregoric**	**octreotide**	**bismuth subsalicylate**
ASSESSMENT AND MONITORING	•Client history; recent travel, antibiotic use, or hospitalization; dietary history •Current symptoms; stool characteristics and frequency; abdominal assessment; signs of dehydration •Vital signs •Laboratory results: stool culture, CBC, electrolytes		
CLIENT EDUCATION	•Explain the purpose of medication •Take as directed •Side effects: constipation and gastrointestinal discomfort •Contact healthcare provider if diarrhea lasts for more than 48 hours or if signs of dehydration develop		
	•May cause dizziness and drowsiness •Do not take with tranquilizers, sedatives, alcohol, or other opioids •Avoid hazardous activities	•Take on empty stomach •Report right upper quadrant pain fever, chills, clay-colored stools	•May cause black stools and/or darken tongue •Do not take with other salicylates