



Drugs for Constipation and Diarrhea

- When bowel movements become less frequent and stools become difficult to pass .
 - It may be due to dehydration , lack of dietary fibre, medication side effects.
 - To promote evacuation of bowels drugs used are;
 - (a) Laxative or aperient:
 - milder action
 - elimination of soft but formed stools.
 - (b) Purgative or cathartic:
stronger action resulting in more fluid evacuation
- Many drugs in low doses act as laxative and in larger doses as purgative.

Pathophysiology :

- Causes of constipation can be divided into primary and secondary
- Most common is primary or functional constipation
- Primary or functional constipation is not due to any underlying cause
- Secondary cause:
 - Immobility
 - Improper diet
 - Endocrine & metabolic disorder
 - Neurological disorder
 - Psychological condition

Medication associated with constipation:

- Aluminum and calcium containing antacid
- Anticholinergic drugs
- anti-depressants
- Anti-psychotic agents
- Iron
- opioids

CLASSIFICATION FOR CONSTIPATION:

1. Bulk forming Dietary fibre:

Bran, Psyllium (Plantago)

Ispaghula, Methylcellulose

2. Stool softener Docusates

(DOSS), Liquid paraffin

3. Stimulant purgatives

(a) Diphenylmethanes

Phenolphthalein, Bisacodyl,

Sodium picosulfate

(b) Anthraquinones (Emodins)

(c) 5-HT₄ agonist Prucalopride

(d) Fixed oil Castor oil

4. Osmotic purgatives

Magnesium salts: sulfate,

hydroxide Sodium salts: sulfate,

phosphate Sod. pot. tartrate

Lactulose

MECHANISM OF ACTION All purgatives increase the water content of the faeces by :

- A hydrophilic or osmotic action, retaining water and electrolytes in the intestinal lumen—increase volume of colonic content and make it easily propelled.
- Acting on intestinal mucosa, decrease net absorption of water and electrolyte; intestinal transit is enhanced indirectly by the fluid bulk.
- Increasing propulsive activity as primary action—allowing less time for absorption of salt and water as a secondary effect.

Bulk forming laxative:

- Dietary fiber : **BRAN**
- Residual product of flour industry which consist of 40% of dietary fiber
- Consist of unabsorbable- cellulose, lignin, pectin, glycoprotein & other polysaccharides

MOA:

Absorbs water in the intestine, swells, increases water content of faeces -- Soften it & facilitates colonic transit

Dietary fiber supports bacterial growth in colon which contribute to faecal mass

- First line approach for most pt of simple constipation.
- Reduces recto sigmoid intraluminal pressure
- Relieves symptoms of irritable bowel syndrome

Drawbacks:

- **Unpalatable**
- **Large quantity 20-40 g/ day**
- **Doesn't soften faeces that present in colon or rectum**

Psyllium & ispaghula

- Contain natural colloidal mucilage

MOA: forms a gelatinous mass by absorbing by water

Largely fermented in colon
increase bacterial mass &
softens the feces

- 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 SOFTENERS:

- DOCUSATES (Diocetyl sodium sulfosuccinate DOSS)
- Anionic detergent: soften stools by decreasing the surface tension of fluid in bowel
- Emulsifies the colonic content and increases penetration of water into the faeces
- Dose: 100-400 mg/day

- Drawback :
- Can disrupt the mucosal barrier and enhance absorption of many non-absorbable drugs
- Liquid paraffin- shouldn't be combined with this
- Cramps and abdominal pain can occur
- Bitter ; liquid preparation may cause nausea

Liquid paraffin :

- It is a viscous liquid mixture of petroleum hydrocarbon
- Uses: soften stools lubricant by coating
- Dose: 15-30 ml/ day oil as such or in emulsified form
- Drawbacks : unpleasant to swallow small amount passes into intestinal mucosa , cause pulmonary edema
- Carries away fat soluble vitamins with it into the stool, deficiency may occur on chronic use.

STIMULANT PURGATIVE:

- **DIPHENYLMETHANES:** Phenolphthalein , Bisacodyl
- Actiavtes in intestine by deacylation
- Site of action is in colon: irritate the mucosa, produce mild inflammation
- Stimulate peristalsis
- Dose : phenolphthalein- 60 to 130 mg & Bisacodyl 5-15 mg
- Drawbacks : allergic reaction , skin rashes fixed drug eruption
- Stevvens johmson syndrome have been developed

Anthraquinones:

Senna is obtained from leaves of certain cassia sp while cascara , sagra da is the powdered bark of the buck- thorn tree

These contain anthraquinone- glycosides also called emodins

MOA:

- In the colon bacteria liberate active anthrol form, which either acts locally or is absorbed into circulation
- Active principle acts on the myenteric plexus to increase peristalsis
- Dose : 12-18 mg

- Drawbacks :
- Skin rashes are occasionally seen
- Regular use for 4-12 months causes mucosal pigmentation.

Prucalpride : (5HT4)

- It has selective 5HT4 receptor agonist marked recently in UK, Europe, Canada for chronic constipation when other laxative fail.
- Activates 5HT4 receptor on intrinsic enteric neurons to promote propulsive contraction in ileum & more prominently in colon.
- Enhance release of excitatory transmitter ACh.
- Colonic transit and stool frequency is improved

Side effects:

Headache abdominal pain

Dizziness diarrhea

Fatigue

Castor oil:

- Bland vegetable oil obtained from the seeds of *Ricinus communis*

MOA:

- Mainly contain triglyceride of ricinoleic acid which is a polar long chain fatty acid
- Castor oil hydrolyzed in the ileum by lipase to ricinoleic acid --- which acts primarily in the small intestine to stimulate secretion of fluid and electrolytes & speed up intestinal transit.
- Adverse effects: frequent cramping, possibility of dehydration

Osmotic purgative: Solute that are not absorbed in the intestine retain water osmotically and distend the bowel by increasing peristalsis indirectly
Magnesium salt also release cholecystokinin which augment motility and secretion ;

- Magnesium hydroxide as 8% w/w suspension (milk of magnesia) 30 ml
- Mag sulfate 5-15 gm
- Sodium sulfate 10-15 gm
- Sodium phosphate 6-12 gm
- Sodium potassium tartrate 8 - 15gm

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

DRAWBACKS:

- ✓ Unpleasant
- ✓ Vomiting
- ✓ Produce watery stool & after constipation

LACTULOSE:

- Disaccharide of fructose & lactose, which is neither digested nor absorbed in the small intestine
- Retain water
- Increased faecal bulk by hydrophilic action
- Also due to osmotic action
- Dose: 10mg BD with plenty of water
- **DRAWBACKS:**
- Flatulance & flatus
- Cramps
- nausea

Diarrhea:

- It is defined by WHO as 3 or more loose or watery stool in a 24 hours period.
- Diarrheal diseases constitute a major cause of morbidity and mortality worldwide
- Types of diarrhea:
 - Acute: sudden onset and lasts for more than 2 weeks
 - Chronic : last for more than 4 weeks
 - Persistent: last between 2 to 4 weeks

Pathophysiology:

- The osmotic load of luminal contents plays an important role in determine final stool water volume.
- inhibition of Na^+/K^+ and structural damage to mucosa cell (by rota virus) cause diarrhea by reducing absorption

Management :

- ✓ treatment of fluid depletion, shock & acidosis
- ✓ Maintenance of nutrition
- ✓ Drug therapy

Rehydration: intravenous or oral route

- Intravenous rehydration is needed when fluid loss is severe (pt is losing more than 10 ml kg/hr)
- Unable to take oral fluids due to weakness, vomiting
- The composition of oral rehydration salt/solution (ORS) has been debated. The general principles are
 - (a) It should be isotonic or somewhat hypotonic,
 - (b) The molar ratio of glucose should be equal to or somewhat higher than Na^+
 - (c) Enough K^+ (15–25 mM) and bicarbonate/ citrate (8–12 mM) should be provided to make up the losses in stool

- New formula WHO-ORS In 2002 a new formula low Na⁺ low glucose ORS was released by the WHO:

New formula WHO-ORS			
<i>Content</i>		<i>Concentrations</i>	
NaCl	: 2.6 g	Na ⁺	— 75 mM
KCl	: 1.5 g	K ⁺	— 20 mM
Trisod. citrate	: 2.9 g	Cl ⁻	— 65 mM
Glucose	: 13.5 g	Citrate	— 10 mM
Water	: 1 L	Glucose	— 75 mM
Total osmolarity 245 mOsm/L			

(available as ORETRAL-A, ELECTROBION, ELECTRAL 21 g sachet for 1000 ml; WALYTE, RELYTE 4.2 g sachet for 200 ml).

Volume equivalent to 10% body weight should be infused over 24 hr ; subsequent rate of infusion is matched with the rate of the fluid loss

Oral rehydration salt : ORS

- ADMINISTRATION OF ORS
- Pt are encouraged to drink ORS at ½-1 hour intervals
- Initially 5-7.5 % vol equivalent is given 2-4 hr(5ml/kg/hr in children)
- ORT is not designed to stop diarrhoea, but to restore and maintain hydration, electrolyte and pH balance until diarrhoea ceases,

SUPER ORS:

- Super ORS are the special types of ORS which instead of Mono- sugar
- Contain more complex sugars
- It may be food based(mostly Rice based ; rice powder) or otherwise starch free(glycine/ alanine) or glucose polymer based

- Advantages :
- Provides rehydration
- Help in reducing stool output, frequency of stool and duration of diarrhea
- With gradual release of glucose prevents secondary disaccharide intolerance
- Disadvantage : short shelf life

Zinc in pediatric diarrhea:

- WHO have recommended that all children with acute diarrhea should be given zinc supplementation with ORS and continued for next 10-14 days
- 20mg/day 6-60 months age
- 10mg/day 0-6 months age
- With ORS decreases the duration and severity of acute diarrhea
- Decreases reoccurrence of diarrhea for next 2-3 months

DRUG THERAPY:

**SPECIFIC
ANTIMICROBI
AL DRUGS**

The diagram features a blue background with three large, stylized arrows pointing to the right. The top arrow is light green and contains the text 'SPECIFIC ANTIMICROBI AL DRUGS'. The middle arrow is light orange and contains the text 'NONSPECIFIC ANTI-DIARRHEAL DRUGS'. The bottom arrow is light blue and contains the text 'PROBIOTICS'. The arrows are arranged in a staggered fashion, with the green and orange arrows starting at the same horizontal level on the left, and the blue arrow starting further to the right.

**NONSPECIFIC
ANTI-DIARRHEAL
DRUGS**

PROBIOTICS

ANTIMICROBIAL : Useful in severe disease

- ✓ Travelers diarrhea mostly due to ETEC(COTRIMOXAZOLE, NORFLOXACIN REDUCES THE DURATION)
- ✓ EPEC: less common(COTRIMOXAZOLE, NORFLOXACIN)
- ✓ Yersinia enterocolitica: common in colder area(COTRIMOXAZOLE)
- ✓ S. Typhimarium enteritis: ciprofloxacin & cotrimoxazole

Probiotics in diarrhea:

- These are the microbial cell preparation (either live culture or lyophilized powder)
- Intended to restore & maintain healthy gut flora
- Recolonization of gut by non-pathogenens
- (mostly lactic acid forming bacteria & yeast is belived to help restore this balance
- Organism most commonly used are ; lactobacillus, Bifidobacterium, yeast-Saccharomyces boulardi)
- probiotics appear to be useful adjuncts to conventional therapy of acute infectious diarrhoea, and are loudly promoted as well as frequently prescribed

Nonspecific antidiarrhoeal drugs

- A. Absorbants and adsorbants
- B. Antisecretory drugs
- C. Antimotility drugs

Absorbants: ispaghula, methyl cellulose, carboxy methyl cellulose

- colloidal bulk forming substances which absorb water and swell
- Modify the consistency and frequency of stools
- increase the consistency of faeces in colostomy patients.
- ispaghula and other bulk forming colloids are useful in both constipation and diarrhoea phases of IBS
- Adsorbants like kaolin, pectin, attapulgite are believed to adsorb bacterial toxins in the gut and coat/protect the mucosa

Antisecretory drugs

- Racecadotri:
- It is a prodrug rapidly converted to thiorphan.
- It is an enkephalinase inhibitor
- It prevents degradation of endogenous enkephalins (ENKs)

MOA:

- decreases intestinal hypersecretion, without affecting motility
- Used in shortterm treatment of acute secretory diarrhoeas
- elimination $t_{1/2}$ as thiorphan is 3 hr\
- Side effects are nausea, vomiting, drowsiness, flatulence.

- **Bismuth subsalicylate:**
- Taken as suspension
- act by decreasing PG synthesis in the intestinal mucosa, thereby reducing Cl^- secretion
- **It has some prophylactic value in travellers' diarrhoea (probably due to weak antibacterial action)**
- Inhibit inflammation by PG inhibition
- Side effects: dark stool
- And black staining of tongue

• Octreotide:

- This somatostatin analogue has a long plasma $t_{1/2}$ (90 min)
- potent antisecretory/ antimotility action on the gut.
- It has been used to control diarrhoea in
 - ✓ carcinoid and vasoactive intestinal peptide (VIP) secreting tumours
 - ✓ for refractory diarrhoea in AIDS patients

but needs to be given by s.c. injection

Side effects:

Short term therapy leads to nausea, bloating and pain in site of injection

Long term therapy leads to gallstone

Antimotility drugs:

- These are opioid drugs which increase small bowel tone
- afford only symptomatic relief in diarrhoea
- major action appears to be mediated through μ opioid receptors
- δ receptors are believed to promote absorption and inhibit secretion, while the μ receptors enhance absorption and decrease propulsive movements

- **Diphenoxylate (2.5 mg) + atropine (0.025 mg): LOMOTIL tab and in 5 ml liquid:**
- It is a synthetic opioid exclusively as constipating agent;
- antidiarrhoeal action is most prominent
- Atropine is added in subpharmacological dose to discourage abuse
- Side effects: Because it is absorbed systemically and crosses blood-brain barrier—CNS effects occur
- caused respiratory depression, paralytic ileus and toxic megacolon in children

- **Loperamide:**

- It is an opiate analogue with major peripheral μ opioid and additional weak anticholinergic property.
- As a constipating agent it is much more potent than codeine.
- Entry into brain is negligible—CNS effects are rare and occur only with high doses
- no abuse liability.
- The duration of action is longer (12 hr) than codeine and diphenoxylate.
- Adverse effects Abdominal cramps and rashes are the most common side effects. Paralytic ileus, toxic megacolon with abdominal distension is a serious complication in young children

