# CONSTIPATION & ANTI-DIARRHOEAL DRUGS

**Subject: Pharmacology-III (BP602)**

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# 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.

# Diagnostic criteria of constipation

❖ 2 or more of criteria listed below:

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

*Criteria fulfilled for the last 3 months with symptom onset.*

## 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 causes:**

- Immobility
- Improper Diet
- Endocrine & Metabolic Disorders
- Neurological Disorders
- Psychological Conditions
- Structural Abnormalities
- Medications

## Medications associated with constipation

- Aluminium and calcium containing antacids
- Anticholinergic agents
- Antidepressants
- Antipsychotics
- Iron
- Opioids

# MANAGEMENT

## DRUGS FOR CONSTIPATION

1. **LAXATIVE :-** milder in action.

2. **PURGATIVE :-** stronger in action.

## CLASSIFICATION

1. **BULK FORMING:-**

   **Dietary fiber** : Bran ,psyllium ,ispaghula ,methylcellulose

2. **STOOL SOFTENER:-**

   Docusates(DOSS), Liquid paraffin

3. **STIMULANT PURGATIVES:-**

(a) Diphenylmethane- Phenolphthalein,Bisacodyl,sodium picosulfate
(b) Anthraquinones (emodins)- senna ,cascara sagrada
(c) 5-$HT_4$ agonist- Prucalopride
(d) castor oil.

4. **OSMOTIC PURGATIVES:-**

- **Magnesium salts**: suflate,hydroxide
- **sodium salts**: sulfate ,phosphate
- sod.pot.tartrate
- lactulose.

## 1. BULK FORMING LAXATIVES

### DIETARY FIBRE:- BRAN

- Residual product of flour industry which consist of 40% of dietary fiber.
- Consist of unabsorbable - cellulose , lignin, pectins,glycoprotiens & other polysaccharides.

### MECHANISM OF ACTION:-

- Absorbs water in the intestines,swells,increases water content of faeces- softens it and facilitates colonic transit.
- Dietary fiber supports bacterial growth in colon which contribute to faecal mass.

- First line approach for most patients of simple constipation.
- Reduces Recto sigmoid intraluminal pressure.
- Relieves symptoms of irritable bowel syndrome (IBS) including pain ,constipation as well as diarrhoea.

**DRAWBACKS**

- Unpalatable
- Large quantity (20-40 g/day) needs
- Does not soften faeces already present in colon or rectum
- Should not be used in patients with gut ulcerations, adhesions.

## 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.

## 2. 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 in to 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

## 3. STIMULANT PURGATIVES

### (a) DIPHENYLMETHANES: Phenolphthalein, Bisacodyl

- Activated in intestine by deactylation
- Site of acton 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.

## (b) ANTHRAQUINONES

- **Senna** is obtained from leaves of certain *Cassia sp.*, while **Cascara, sagrada** is the powdered bark of the buck-thorn tree.
- These contain anthraquinone-glycosides ,also called *Emodins*.

**MACHANISM 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).

## (c) PRUCALOPRIDE

- It is a selective 5-$HT_4$ receptor agonist marketed recently in UK, Europe and Canada for chronic constipation, when other laxative fail.
- It activates 5-$HT_4$ 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.

## (d) CASTOR OIL

- Castor oil is a bland vegetable oil obtained from 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).

## 4. 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 faecal bulk by hydrophilic action and also due to osmotic action.

**DOSE:**

- 10 mg BD with plenty of water

**DRAWBACK:**

- Flatulance and flatus is common, cramp also occur.
- Nausea due to its peculiar sweet taste.

# DIARRHOEA

- It is defined by WHO as 3 or more loose or watery stool in a 24 hour period.
- Diarrhoeal diseases constitute a major cause of morbidity and mortality worldwide; especially in developing counties.
- Globel burden of pediatric diarrhoea is estimated to be1.5 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 undernutrition.

# 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

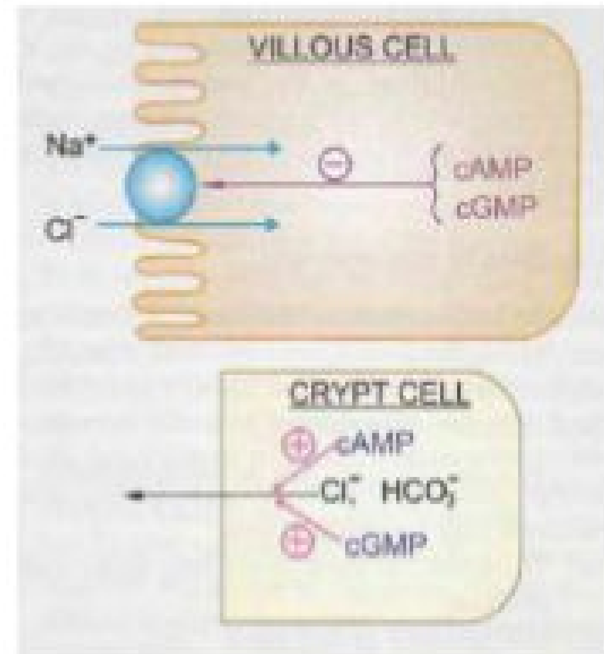
## PATHOPHYSIOLOGY

- The osmotic load of luminal contents plays an important role in determining final stool water volume.
- When nonabsorbable solutes are present and in disaccharidase deficienry (which occurs during starvation), the stool water is increased.
- Inhibition of $Na^{+}K^{+}$ATPase and structural damage to mucosal cell (by Rota virus) causes diarrhoea by reducing absorption.

## CONTD……

- Intracellular cyclic nucleotides are important regulators of absorptive and secretory processes.

- Stimuli enhancing cAMP or cGMP cause net loss of salt and water, both by inhibiting NaCl absorption in villous cells and by promoting anion secretion in the crypt cells which are primarily secretory.



# MANAGEMENT

For the treatment of 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 | 85mM = 5g | in 1L of water |
| KCl | 13 mM = 1 g | or 5% glucose |
| $NaHCO_3$ | 48mM = 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.

# DRUG THERAPY

- Drug used in diarrhea can be categorized in to

1. Specific antimicrobial drugs
2. Probiotics
3. Nonspecific antidiarrhoeal drugs

A . Antimicrobials are of no value : In diarrhoea due to non infective causes.

- Irritable bowel syndrome (IBS)
- Coeliac disease
- Pancreatic enzyme deficiency
- Thyrotoxicosis
- Rotavirus.

## B. ANTIMICROBIAL ARE USEFUL ONLY IN SEVERE DISEASE

(i) Travelers diarrhoea :mostly due to ETEC , campylobacter: cotrimoxazole, norfloxacin reduces the duration.

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

(iii) Yersinia enterocolitica :common in colder places ,cotrimoxazole is the most suitable drug in severe cases.

(iv) Shigella enteritis:only when associated with blood and mucus in stools may be treated with ciprofloxacin or norfloxin.

(v) Salmonella typhimurium enteritis is often invasive ; severe cases may be treated with ciprofloxacin or cotrimoxazole

## 2. PROBIOTIC IN DIARRHOEA

- These are microbial cell preparation, either live culture or lyophillised powder, that are intended to be restore and maintain healthy gut flora.
- Diarrhoeal 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.and the yeast Saccharomyces boulardii.

# 3. NONSPECIFIC ANTIDIARRHOEAL AGENTS

| | |
|---|---|
| ABSORBANTS | ▪ ISPAGHULA<br>▪ PSYLLIUM<br>▪ METHYLCELLULOSE |
| ANTISECERTORY | ▪ RECECADOTRIL<br>▪ BISMUTH SUBSALICYLATE<br>▪ ANTICHOLINERGICS<br>▪ OCTREOTIDE |
| ANTIMOTILITY | ▪ CODEINE<br>▪ DIPHENOXYLATE<br>▪ 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)

### MACHANISM 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 remains poorly understood, it is thought to act by

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

-Reducing inflammation/irritation of stomach through inhibition of prostaglandin

- for the prevention and treatment of traveller's diarrhoea, but it also is effective in other forms of episodic diarrhoea.

## DOSE

- Taken as suspension 60 ml 6 hourly.

## DRAWBACK

- Dark stools and black staining of the tongue.

## 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.

## Diphenoxylate

- Synthetic opioids,used exclusively As anti-diarrheal agents.
- available in preparations containing small doses of atropine to discourage abuse.

**DOSE**

- 25 µg atropine sulfate with 2.5 mg diphenoxylate
- usual dosage is two tablets initially, then one tablet every 3-4 hours, not to exceed eight tablets per day.

**DRAWBACK**

- produce CNS effects when used in higher doses (40-60 mg per day) and thus have a potential for abuse and/or addiction.
- Respiratory depression, constipation.

## LOPERAMIDE

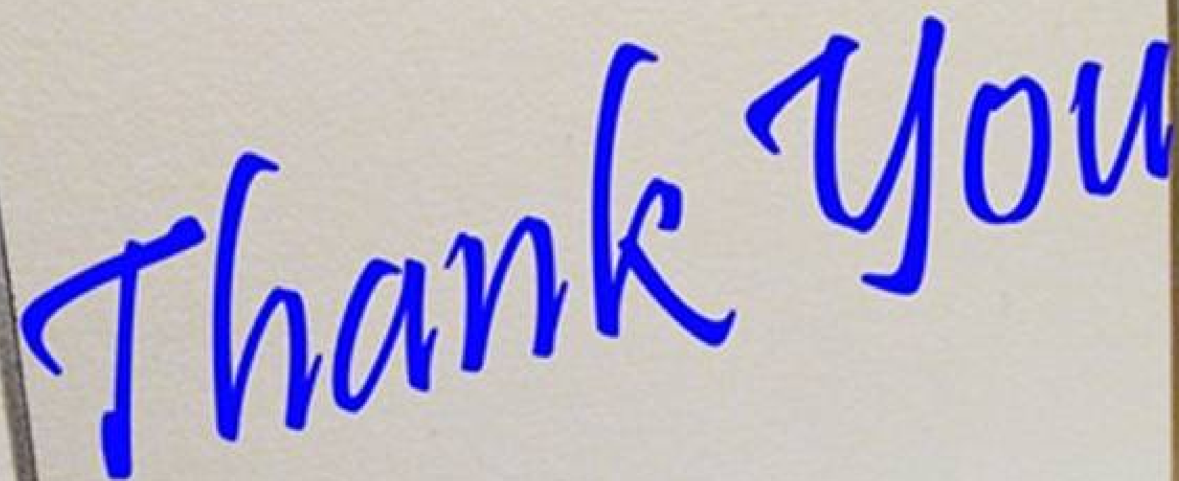
- It is an opiate analogue with major peripheral opioids and additional weak anticholinergic property.
- Loperamide also has anti-secretory activity against cholera toxin and some forms of *Escherichia coli* toxin, presumably by acting on $G_i$-linked receptors and countering the increase in cellular 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.


Thank You