

## Management of Constipation.

Kamlesh Garg, C. D. Tripathi

Department of Pharmacology, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India

**Abstract:** Chronic constipation is common clinical problem having higher prevalence rate in women. Treatment of constipation depends upon the underlying primary or secondary cause. Most of the patients present with idiopathic/functional chronic constipation. Life style and dietary modifications can treat constipation in majority of such patients. Pharmacotherapy should be started only if the non-pharmacological measures fail. Drugs used for functional constipation are: bulk laxatives (psyllium), osmotic laxatives (magnesium citrate), emollients (liquid paraffin), Stool softeners (docusate sodium) and stimulant purgatives (cascara). Lubiprostone is used to treat chronic idiopathic constipation, enteric neuropathy and irritable bowel syndrome with constipation (IBS-C). Methylnaltrexone is one of the newer agents of peripherally-acting  $\mu$ -opioid antagonists which were approved for the treatment of opioid induced constipation. Prucalopride is a drug licensed for women with chronic constipation who have not responded to conventional laxatives. Linaclotide is an emerging drug that has shown promise in improving bowel function in chronic constipation and IBS-C with minimal side effects.

### INTRODUCTION

Chronic constipation may be associated with variety of long standing conditions and drug therapies or it may be idiopathic<sup>1</sup>. Management of constipation depends upon the cause. Constipation due to some underlying local cause like colorectal neoplasia, intestinal obstruction, hemorrhoids, fissure or inflammatory bowel disease is treated by eliminating the cause. Besides these, constipation secondary to either endocrine cause (Hypothyroidism or Diabetes mellitus) or neurological cause (Multiple sclerosis, Parkinsonism) is self treated by correction of secondary cause. Stoppage of therapy with the drugs causing constipation like anticholinergics, opioids, calcium channel blockers, antispasmodics should be done, if constipation is drug-induced<sup>2</sup>.

Most patients present with idiopathic constipation. Treatment of such patients should be initiated with either diet or non-pharmacological measures. Drug treatment should be started only if the non-pharmacological measures fail.

### NON PHARMACOLOGICAL MEASURES

Patient should be reassured and educated regarding proper diet, daily water intake, regularity and timing of bowel movements. Patients should also be discouraged to postpone the urge of defecation. Increase in dietary fiber in the form of cereals, grains fruits, vegetables and increased water intake helps in increasing the bulk of stools. Recommended daily intake of dietary fiber is 30 grams. In the patients having dietary fiber deficiency can be given fiber supplements like psyllium. Patients should also be encouraged to adapt active life style as increasing physical activity promotes colonic motility<sup>2</sup>.

### DRUG TREATMENT OF CONSTIPATION

Drug treatment should be started in those patients who fail to respond to non-pharmacological measures. There are various classes of drugs used in treatment of constipation as classified in table I. The choice of treatment is based upon etiology of constipation, mechanism, onset and duration of action of the drug<sup>2</sup>.

1. **Bulking agents:** The bulking agents are often the first line of treatment. Hydrophilic organic polymers (psyllium, bran, ispaghula, methylcellulose, calcium polycarbophil) are included in this category. **Mechanism of action:** All the bulking agents contain dietary fiber. Dietary fiber is that part of food which is resistant to enzymatic degradation and it is presented to colon in unchanged form where it is fermented by colonic bacteria. Fermentation of fiber results in either

production of short chain fatty acid (have prokinetic effect) or increase in bacterial mass (contribute to increased stool volume). Fermented fiber can attract water and increases stool bulk. Wheat bran with high lignin (insoluble and poorly fermentable fiber) having > 40% dietary fiber is most effective in increasing stool volume. Psyllium husk contains a hydrophilic mucilloid that undergoes significant fermentation in colon leading to increase in colonic bacterial mass. Methylcellulose and polycarbophil are poorly fermentable fibers which act by increasing water absorption and increasing fecal mass. **Adverse effects:** Bloating and abdominal pain due to fermentation of fiber. Calcium polycarbophil preparations can release calcium in gastrointestinal tract.

**Contraindications:** Bulk forming agents are contraindicated in mega colon, mega rectum and obstructive symptoms.

**Indication:** Bulking agents are first line of treatment for simple and functional constipation. These agents can also be used to relieve symptoms of irritable bowel syndrome and colonic diverticulosis<sup>3, 4</sup>.

2. **Stool softeners:** Stool wetting agents such as Docusate are anionic surfactants that lower the surface tension of stool to allow mixing of aqueous and fatty substances which softens the stool and permits easier defecation. Sodium, calcium, potassium salts of docusate are available for use. These agents also stimulate intestinal fluid and electrolyte secretion and alter intestinal mucosal permeability. These drugs are specially indicated when straining at stools must be avoided. **Adverse effects:** Nausea, cramps and abdominal pain<sup>3, 4</sup>.
3. **Emollients (Lubricants):** Mineral oil and liquid paraffin, have no pharmacological interaction with colonic mucosa but alters the composition of stool. Lubricants are not preferred for regular use because of certain side effects like malabsorption of fat soluble vitamins, foreign body reactions in intestinal mucosa and aspiration of oil leading to lipid pneumonitis<sup>3, 4</sup>.
4. **Osmotically active agents:** Drugs included in this category are Saline laxatives (Magnesium sulphate, Magnesium hydroxide, Magnesium citrate, Sodium phosphate), non digestible sugars and alcohols (glycerine, lactose, sorbitol and mannitol) and polyethylene glycol (PEG) electrolyte solutions.

**Mechanism of action:** The cathartic action of these agents results from osmotically mediated water retention. The water retention stimulates peristalsis and usually produces a bowel movement in 1-3 hours. PEG's - Polyethylene glycol electrolyte solutions are absorbed poorly and retain added water by virtue of their high osmotic nature.

**Precautions:** Among saline purgatives, Magnesium and Phosphate containing preparations are well tolerated in most patients but they

need to be given with caution in patients with renal insufficiency, cardiac disease and in patients on diuretic therapy. During treatment, monitoring of electrolytes is mandatory for these patients. Non-fermentable sugars should not be used in diabetic people.

**Adverse effects:** Abdominal discomfort and Flatulence.

**Use:** Osmotic laxatives are employed in high dosage for rapid cathartic effect and in lower dosage for laxative effect. Lactulose and sorbitol are effective in treatment of idiopathic, opioid and vincristine induced constipation and in elderly. Polyethylene glycol electrolyte solutions are used as cathartics either prior to bowel procedures or constipation in difficult cases<sup>2,3,4</sup>.

5. **Stimulant (Irritant) Laxatives:** Drugs included in this group are Diphenylmethane derivatives (bisacodyl, phenolphthalein), Anthraquinones (senna, aloe, cascara) and Ricinoleic acid.

**Mechanism of action:** Stimulant laxatives cause accumulation of water and electrolyte and stimulate intestinal motility. These effects are mediated by activation of Prostaglandins/cyclic AMP and nitric oxide/cyclic GMP pathways. Bisacodyl is available as enteric coated oral tablet and in the form of suppository. Laxative effects are produced within 6-10 hours and 30-60 minutes with oral and rectal bisacodyl respectively.

**Adverse drug effects:** Excessive fluid secretion and cramps can occur. Cathartic colon and melanosis coli can occur on prolonged use with anthraquinones. Castor oil is not used frequently because of its unpleasant taste as well as its potential toxic effects on intestinal epithelium.

**Indication:** Stimulant laxatives are useful in patients with poor colonic motility and often combined with stool softeners<sup>3</sup>.

*Newer drugs for treatment of constipation*

6. **Lubiprostone:** Lubiprostone (marketed under the trade name Amitiza) was approved by U.S. Food and Drug Administration (FDA) in 2006 and 2008 to treat chronic idiopathic constipation, enteric neuropathy and irritable bowel syndrome with constipation (IBS-C) respectively.

**Mechanism of action:** Lubiprostone is an oral bicyclic fatty acid that selectively activates type 2 chloride channels in the apical membrane of human gastrointestinal epithelial cells, thereby increasing chloride-rich fluid secretion. These secretions soften the stool, increase motility and promote spontaneous bowel movements. The intestinal transit time is decreased and symptoms of constipation like pain and bloating are alleviated.

**Dose:** In IBS-C a dose of: 8µg twice daily is recommended.

**Adverse effects:** In clinical trials, most of the side effects were being of mild to moderate severity. The most common adverse event was nausea (31%). Other adverse events included diarrhea, headache, abdominal distention, abdominal pain, flatulence, sinusitis and vomiting.

**Contraindications:** Lubiprostone is contraindicated in patients exhibiting chronic diarrhea, bowel obstruction, or diarrhea-predominant irritable bowel syndrome. There are no current data on use in patients with hepatic and/or renal complications. The effects on pregnancy have not been studied in humans but testing in Guinea pigs resulted in fetal loss.

**Indications:** Lubiprostone is used to treat chronic idiopathic constipation, enteric neuropathy and irritable bowel syndrome with constipation (IBS-C). In addition, a randomized, 4-week withdrawal period at the end of one of the phase III trials demonstrated that discontinuation of lubiprostone was not associated with rebound of symptoms of irritable bowel syndrome<sup>5</sup>.

7. **Methylnaltrexone** (trade name Relistor) is one of the newer agents of peripherally-acting µ-opioid antagonists which was approved by

the US FDA on April 24, 2008 for the treatment of opioid induced constipation.

**Mechanism of action:** Methylnaltrexone binds to the same receptors as opioid analgesics such as morphine, but it acts as an antagonist, blocking the effects of those analgesics, specifically the constipating effects on the gastrointestinal tract without reversing the analgesic properties of opioid agonists or causing withdrawal symptoms. Furthermore, as methylnaltrexone cannot cross the blood-brain barrier, it is formed by N-methylation of the uncharged naltrexone making it incapable to cross blood-brain barrier because of its polarity and low lipid solubility<sup>6</sup>.

**Adverse effects:** Abdominal pain and flatulence

**Dose:** 0.15–0.3 mg/kg. by subcutaneous route. Oral formulation of methylnaltrexone for opioid induced constipation in patients of chronic pain is being developed.

**Use:** Methylnaltrexone is approved for the treatment of opioid induced constipation in patients with advanced illness. It is generally only to be used when ordinary laxatives have failed. This drug is not effective if constipation is not opioid induced<sup>6,7</sup>.

8. **Prucalopride :** It is a new drug licensed for women with chronic constipation who have not responded to conventional laxatives. It is not yet licensed for use in men because 90% of the participants in clinical trials were women and there is evidence that efficacy of the drug at recommended dose is greater in women. Clinical trials in men are being carried out.

**Mechanism of action:** Prucalopride is a selective 5-HT<sub>4</sub> agonist. Clinical trials have shown that Prucalopride increase intestinal transit, improves the frequency of bowel movements and patient's satisfaction with the defecatory function.

**Adverse effects:** Headache, nausea, abdominal pain and diarrhea.

**Dose:** The recommended dose of Prucalopride is 1-2 mg once daily. In elderly dose is 1 mg per day.

**Contraindications:** Prucalopride is contraindicated in patients with intestinal obstruction, ileus or inflammatory bowel disease. This drug should be used with caution in patients taking drugs which may prolong QT interval like erythromycin.

**Indication:** Prucalopride is a new therapeutic option for treatment of chronic constipation in females failing conventional treatment with osmotic and stimulant laxatives<sup>1</sup>.

9. **Linaclotide:** It is an emerging drug that has shown promise in improving bowel function in chronic constipation with minimal side effects.

**Mechanism of action:** Linaclotide is a 14-amino-acid peptide that is minimally absorbed in the gut, is thought to bind to and activate the guanylate cyclase C receptor on the luminal surface of intestinal enterocytes, thus increasing cyclic GMP levels and triggers a signal transduction cascade that activates the cystic fibrosis transmembrane conductance regulator which stimulates intestinal fluid secretion.

**Efficacy:** Linaclotide has been investigated as a treatment for chronic constipation and constipation-predominant irritable bowel syndrome. Phase I data demonstrated that the drug is safe and well tolerated up to 3000µg doses. Authors from phase II trials (at doses 75 µg, 250 µg, 300 µg, and 600 µg) have reported that 28 days of linaclotide treatment significantly improved the weekly rate of spontaneous bowel movements (SBMs). Linaclotide also significantly improved patient's secondary symptoms (like weekly rates of complete SBMs, stool consistency, straining, abdominal discomfort and bloating) as well as global measures of constipation and quality of life. Treatment was followed by a 14-day washout period, during which the actively treated group did not experience any rebound effect of stopping linaclotide on chronic constipation. Phase III trials are being planned for this

**Table 1:** Comparison of different agents in treatment of constipation

S.No.	Drug	Mechanism of action	Time of onset of action	Effect on consistency of stools	Adverse effects	Indication
1	<b>Bulking agents</b> <sup>3,4</sup> (Psyllium, bran, Ispaghula, Methylcellulose, Calcium Polycarbophil)	Absorption of water in intestine	1-3 days	Softening of feces	Bloating and abdominal pain	Functional constipation, irritable bowel syndrome and colonic diverticulosis
2	<b>Stool softeners</b> <sup>3,4</sup> (Docusate salts)	Accumulation of water in intestinal lumen	1-3 days	Softening of stools	Nausea, cramps and abdominal pain	To avoid straining at stools
3	<b>Emolients /Lubricants</b> <sup>3,4</sup> (Mineral oil, liquid paraffin)	Alters the composition of stool.	3-4 hours(oral) 30-60 minutes (rectal)	Softening of feces	Bloating and abdominal pain	Used to lubricate hard scybali
4	<b>Osmotically active agents</b> <sup>2,3,4</sup> (Saline laxatives, non-digestible sugars, polyethylene glycol)	Osmotically mediated water retention.	1-3 hours	Watery evacuation	Abdominal discomfort and Flatulence	In elderly, idiopathic, opioid and vincristine induced constipation, prior to bowel procedures and after purge
5	<b>Stimulant /Irritant Laxatives</b> <sup>3</sup> (Bisacodyl, senna, aloe, cascara)  Castor oil	Accumulation of water and electrolytes in intestinal lumen	6-8 hours  1-3 hours	Soft or semifluid stools  Watery evacuation	Cramps and excessive fluid secretion  Unpleasant taste and toxic to intestinal epithelium	In patients with poor colonic motility  Rarely indicated
6	<b>Lubiprostone</b> <sup>5</sup>	Activates type 2 chloride channels in intestinal epithelium	24 hours	Softening of stools	Nausea, diarrhea, abdominal pain, headache and flatulence	chronic idiopathic constipation, enteric neuropathy, IBS-C
7	<b>Methylnaltrexone</b> <sup>6,7</sup>	Peripherally-acting $\mu$ -opioid antagonist	1-4 hours	Softening of stools	Abdominal pain and Flatulence	Opioid Induced Constipation
8	<b>Prucalopride</b> <sup>1</sup>	Selective 5-HT <sub>4</sub> agonist.	—	Increases spontaneous bowel movements	Headache, nausea, abdominal pain and diarrhea.	Chronic constipation in females
9	<b>Linaclotide</b> <sup>8</sup>	Activates guanylate cyclase C receptor and stimulates intestinal fluid secretion	24 hours	Increases spontaneous bowel movements	Diarrhoea and nausea	Chronic constipation and IBS-C

drug at doses 150  $\mu$ g and 300  $\mu$ g.

**Adverse effects:** Diarrhea and nausea <sup>8</sup>.

## MANAGEMENT OF CONSTIPATION IN PREGNANCY

Constipation is a common complaint in late pregnancy and its prevalence is reported to be 11-38%, the likely cause is rising levels of circulating progesterone. First line therapy for treatment of constipation in pregnancy includes increasing fiber intake through diet or supplements. Adding more fiber to the diet increases the frequency of defecation and leads to softer stools. Fiber supplements are effective and cause no serious side effects to mother or fetus. The short-term use of osmotic or stimulant laxatives is generally reserved for the patients who fail to respond to dietary changes or bulking agents. Reports of clinical trials have shown that stimulant laxatives are more effective than bulking agents but may cause adverse effects such as diarrhea and abdominal pain. Side effects of stimulant laxative have reduced their acceptability to patients. The beneficial effects of the drug used for treatment of constipation during pregnancy must be weighed against its possible adverse effects because most laxatives carry a pregnancy category B or C category <sup>9, 10</sup>.

## MANAGEMENT OF CONSTIPATION IN CHILDREN

For children having acute onset of constipation dietary measures including increase in fluid, carbohydrate and dietary fiber should be recommended. The normal intake of dietary fiber should be patient age +5 grams per day. Various laxatives used to treat constipation in children are: Psyllium, Mineral oil, Osmotic agents (Lactulose, Barley meat extract, Sorbitol, Magnesium hydroxide, Polyethylene glycol 3350, Polyethylene glycol electrolyte solution), Stimulants (Senna, Bisacodyl) and Phosphate

enemas. Enemas should be avoided in infants. Children should be discouraged to do intentional fecal withholding. Children and parents should be educated about the benefits of regularity and time specificity of defecation. Defecation after meals is recommended so as to take advantage of gastro-colic reflex. Training of establishment of regular bowel habit may need to be continued along with treatment with laxative. Once the regular bowel pattern is established, laxative should be slowly weaned off and thereafter patient is encouraged to go for dietary management <sup>11</sup>. In conclusion, management of constipation depends upon the primary or secondary cause. In chronic idiopathic/functional constipation, when non-pharmacological measures fails, initial choice of laxative is bulk forming agent; which may be supplemented or replaced by an osmotic and/or a stimulant laxative in resistant cases. Long term therapy with bulking agents, polyethylene glycol or lactulose is considered to be safe but long term use of stimulant laxatives should be avoided because of adverse effects <sup>1, 2</sup>.

## REFERENCES

- Chaplin S, Blaker P and Wilkinson. Prucalopride (Resolor): New drug for chronic constipation. *Prescriber* 2010;21:24-29.
- Selby W and Corte C. Managing constipation in adults. *Australian Prescriber* 2010;33:116-19.
- Pasricha PJ. Treatment of disorders of bowel motility and water influx, antiemetic; agents used in biliary and pancreatic disease. In: Goodman and Gillman's the pharmacological basis of therapeutics, 11<sup>th</sup> ed. (Bruton, Lazo and Parker eds). Mc Grav Hill, New York 2006;983-1008.
- Tripathi KD. Drugs for constipation and diarrhea. In: Essentials of medical pharmacology, 6<sup>th</sup> ed. (Tripathi ed), Jaypee Brothers, New Delhi 2008;651-64.
- Carter NJ and Scott LJ. Lubiprostone: in constipation-predominant irritable bowel syndrome. *Drugs* 2009;69:1229-37.
- Thomas J, Karver S, Cooney GA, Chamberlain BH, Watt CK, Slatkin NE et al. Methylnaltrexone for opioid-induced constipation in advanced illness. *The New England journal of Medicine* 2008;358: 2332-43.
- Slatkin N, Thomas J, Lipman AG, Wilson G, Boatwright ML, Wellman C et al. Methylnaltrexone for Treatment of Opioid-Induced Constipation in Advanced Illness Patient. *J Support Oncol* 2009;7:39-46.
- Harris LA. Constipation: Linaclotide—a stimulating new drug for chronic constipation. *Nature Reviews Gastroenterology and Hepatology* 2010;7:365-366.
- Prathe CM. Pregnancy related constipation. *Current gastroenterology reports* 2004;6:402-04.
- Jewell D and Young G. Interventions for treating constipation in pregnancy. *Cochrane database of systemic reviews* 2001; issue 2, No. CD001142. doi:10.1002/14651858.CD001142.
- Croffie JM. Constipation in children. *Indian J Pediatr* 2006;73:697-701.