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Review Article

Pharmacological Management of Functional Constipation

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Abstract

Constipation is among one of the most common symptoms encountered in clinical practice. Management guidelines and recommendations are limited and are not sufficiently current to include treatments that become available more recently. In this clinical review we aim to present available evidence to guide pharmacological treatment of bulking agents, osmotic and stimulant laxatives, probiotics, prokinetics, calcium channel activators, guanylate cyclase C receptor agonists, bile acid transport inhibitors as well as enemas and suppositories in the management of functional constipation.

Keywords: *Functional Constipation; Bulking Agents; Laxatives; Prokinetics; Calcium Channel Activators; Guanylate Cyclase Agonists; Bile Acid Transport Inhibitors*

Abbreviations

IBS-C: Irritable Bowel Syndrome with Constipation; FC: Functional Constipation; PEG: Polyethylene Glycol; RCT: Randomised Controlled Trial; 5-HT 4R: 5-Hydroxytryptamine Receptor 4

Introduction

Constipation is a common gastrointestinal disease which could have a major impact on quality of life as a result of chronic and disabling symptoms as well as on costs to individual patients and society in general. Estimates of the prevalence of constipation range from 10% to 15% in North America [1]. In a survey administered to an Asian population, the prevalence of chronic constipation was reported as 15 - 23% of female respondents and 11% of male respondents [2].

Constipation is a symptom which is classified as either functional (primary or idiopathic) or secondary to other conditions (neuropathies, drugs, metabolic, structural, myopathies, psychological and immobility). Rome III criteria (Table 1) are used to diagnose functional constipation while secondary constipation is less well defined [3]. The Rome III criteria does not permit a patient who met criteria for irritable bowel syndrome with constipation (IBS-C) to be diagnosed with functional constipation (FC). The recently released update to the Rome diagnostic criteria (Rome IV) make no significant changes to the diagnostic criteria for IBS-C and FC. Although the experts concluded, based on a review of recent new data, that IBS-C and FC are probably different parts of a spectrum of symptoms of constipation rather than distinct disorders, they did not modify the Rome III approach of classifying these as independent, and mutually exclusive diagnoses [4]. Other evidence suggests that practicing gastroenterologists may not regard FC and IBS-C as mutually exclusive diagnoses [5]. A recent study may be remembered as a turning point in the controversy over whether FC and IBS-C are two distinct disorders or parts of a spectrum of symptoms related to a shared pathophysiology. This study was able to show significant differences between well-characterized groups of patients with FC and IBS-C in whole gut transit time, colonic motility, water content in the small intestine, and colon volumes using validated, novel and non-invasive magnetic resonance imaging techniques [6].

1. Must include 2 or more of the following symptoms: a. Straining during at least 25% of toilet visits b. Lumpy or hard stools in at least 25% of defecations c. Sensation of incomplete emptying for at least 25% of defecations d. Sensation of anorectal obstruction/blockage for at least 25% of defecations e. Manual manoeuvres to facilitate at least 25% of defecations f. Fewer than 3 defecations per week.
2. Loose stools are rarely present without the use of laxatives.
3. Symptoms do not fit the criteria for irritable bowel syndrome.
4. Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to the diagnosis.

Table 1: *Definition of chronic constipation according to the ROME III criteria.*

Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to the diagnosis.

Pathophysiological mechanisms for the symptoms of functional constipation

The pathophysiology of FC is multifactorial and incompletely understood. Several sub-types of primary constipation are recognized, however, patients can display symptoms consistent with those from several sub-types.

Delayed whole gut transit

The mechanism believed to account for infrequent passage of stools is impaired peristaltic motility in the colon or small intestine due to decreased amplitudes and/or non-peristaltic patterns of contractions and/or deficient numbers of high-amplitude aborally propagating contractions [7]. However, intestinal motility is difficult to measure directly therefore, so the time required for transit of indigestible markers or radioisotopes is used as a surrogate marker of abnormal intestinal motility.

Pelvic floor dysfunction

The symptom of difficult evacuation of stool from the rectum is often attributed to one of two mechanisms:

- A- Paradoxical contraction or failure to relax the pelvic floor muscles
- B- Inadequate increases in rectal pressure during attempts to defecate.

Many terms have been used to characterize this phenomenon e.g. anismus, pelvic floor dyssynergia or dyssynergic defecation. However, the Rome IV criteria use the umbrella term, functional defecation disorder, to refer to difficult defecation from either cause i.e. dyssynergic defecation or inadequate rectal propulsion [8]. Dyssynergic defecation or inadequate rectal propulsion [8]. Dyssynergic defecation and inadequate rectal propulsion are usually assessed by anorectal manometry or by pelvic floor electromyography. The balloon evacuation test is a measure of the time required for subjects to evacuate a water- or air-filled balloon from the rectum, and it is regarded as a measure of pelvic floor dysfunction [9].

Normal Transit Constipation

Normal-transit constipation is probably the most common form of constipation seen by general clinicians, although this has not formally been studied. Stool traverses at a normal rate through the colon and stool frequency may be normal, but patients feel constipated. On investigation, some patients in this group may have increased rectal compliance, reduced rectal sensation or both [10].

Bulking agents

Bulking agents are fibre supplements including psyllium, calcium polycarbophil, methylcellulose and bran. First-line management in FC as recommended in British, American, European and other global guidelines, as well as expert commentaries, is fibre supplementation [11-14]. Mechanism of action of fibre is believed to be fermentation of fibre in the distal small bowl and colon producing short chain fatty acids and gas influencing gastrointestinal function and sensation. Good laxative effects are observed in intermediate soluble fermentable fibres (e.g. psyllium and oats), insoluble slowly fermentable fibres (e.g. wheat, bran, fruit, and vegetables) and insoluble non-fermentable fibres (e.g. cellulose and sterculia) [15]. Compared with placebo, bulking agents (especially psyllium) resulted in improvements in global symptoms of straining, pain on defecation, and stool consistency, an increase in the mean number of stools per week, and a reduction in the number of days between stools [16].

Potential adverse effects of bulking agents include gas, bloating, oesophageal obstruction, colonic obstruction, and calcium and iron malabsorption. Even though bulking agents are recommended as first line pharmacological agents in FC, psyllium is not effective in severe slow transit constipation or pelvic floor dysfunction. The use of osmotic laxatives may be favoured before initiating treatment of bulking agents to avoid abdominal discomfort, bloating, and pain in this subset of constipated patients [15].

Contraindications for bulking agents include hypersensitivity to any included components, faecal impaction and bowel obstruction. When bulking agents are used, inadequate fluid intake can result in abdominal gas or bloating, which may then paradoxically predispose the patient to bowel obstruction [17].

Magnesium salts

Magnesium salts have been widely used in mild-to-moderate constipation because of their low price and ready availability. It has been shown to be safe and effective [12]. Mechanism of action is by luminal water binding. There are no contraindications but precautions are needed with disease related concerns such as renal impairment or neuromuscular disease. Hypermagnesemia has been described in patients with renal disease as well as in patients with normal renal function [18,19].

Nonabsorbable carbohydrate

Nonabsorbable carbohydrates, such as sorbitol and lactulose, pass unchanged into the colon to be metabolized by colonic bacteria into lactic, acetic, and formic acids, with the liberation of carbon dioxide. These low molecular weight organic acids increase intraluminal fluid osmotically. Lactulose is a prebiotic carbohydrate that stimulates the growth of health-promoting bacteria in the human gastrointestinal tract [20]. The time of onset of lactulose's effect is between 24 and 72 hours.

Nonabsorbable carbohydrates often cause gastrointestinal symptoms, including flatulence, bloating intestinal cramps, nausea, and diarrhoea. Gastrointestinal side effects occur most often with lactulose due to its metabolism by colonic bacteria but these events are usually temporary. No potential serious side effects have been found in patients treated with lactulose for more than 4 weeks, long-term treatment with this agent is generally regarded as safe and well tolerated [21,22].

Polyethylene glycol

Polyethylene glycol (PEG) is a nonabsorbable and nonmetabolized polymer that draws fluid into the intestinal lumen. PEG is poorly absorbed systemically, and does not appear to be associated with an increased risk of malformations in pregnant women [23]. There is reliable evidence for the use of PEG, with several well-designed placebo-controlled randomized trials demonstrating significant benefits of PEG in improving bowel frequency and stool consistency. Numerous trials have shown both electrolyte-enriched PEG and electrolyte-free PEG to be effective in patients with chronic constipation [22,24-27]. PEG with electrolytes is preferred by patients because of its properties such as taste and smell [28]. A meta-analysis involving 10 RCTs found that PEG was better than lactulose with respect to the outcomes of stool frequency per week, form of stool, relief of abdominal pain, and the need for additional products. Although there have been reports about common adverse events including diarrhoea, abdominal pain, nausea, and vomiting, no serious adverse events have been reported with long-term PEG treatment [29].

Stimulant laxatives

Stimulant laxatives represent a diverse class of agents derived primarily from anthraquinones (senna) and diphenylmethanes (bisacodyl and sodium picosulfate), and acting through direct contact with the submucosal plexus and the deeper myenteric plexus, resulting in predominantly motor but also secretory effects on the bowel. The onset of action of bisacodyl is 6-12 hours after oral administration and the onset of action of senna is usually 1-3 hours. In randomized, placebo-controlled trials of sodium picosulfate and oral bisacodyl, it was reported that these agents increased the number of spontaneous bowel movements per week, improved the stool consistency, and decreased the constipation-related symptoms [30,31].

It has been reported that stimulant laxatives are associated with significant adverse events, including malabsorption, electrolyte disturbance, dose-dependent cramping, diarrhoea, abuse, and development of melanosis coli. Cathartic colon is seen in some chronic users of stimulant laxatives, but it is unclear whether this is related to their prolonged use. Thus, stimulant laxatives may be used when patients fail to respond adequately to bulk or osmotic laxatives [32-34].

Probiotics

Probiotics are defined as live microorganisms which, when administered in adequate amounts, confer a health benefit on the host. A systematic review of RCTs to evaluate the efficacy and safety of probiotic supplementation for the treatment of constipation suggested a favourable effect of treatment with *Bifidobacterium lactis* DN-173 010, *Lactobacillus casei* Shirota, and *Escherichia coli* Nissle 1917 on defecation frequency and stool consistency [35]. To achieve the same health benefits seen in clinical trials, probiotics should be administered with specific strains, at specific doses, at specific doses, in specific populations of people. Probiotics can be considered for use in conjunction with other drugs in the treatment of chronic constipation [30].

Prucalopride

Prucalopride is a highly selective 5-hydroxytryptamine receptor 4 (5-HT 4R) agonist with enterokinetic effects. Its high affinity and selectivity for 5-HT 4R differentiates it from previous-generation compounds and minimises the potential for target-unrelated side effects [36]. In healthy human subjects, Prucalopride accelerates colonic transit but does not alter gastric or small bowel transit [37]. Prucalopride, 2 mg once-daily treatment over 12 weeks, was more efficacious than a placebo in improving stool frequency and stool consistency, decreasing the need for rescue medications, reducing the symptoms of constipation in Asian and non-Asian women, and was found to be safe and well-tolerated [38-42]. Recently, Prucalopride was more efficacious than placebo in improving stool frequency and life quality in men with chronic constipation, and was found to be safe and well-tolerated [43].

Prucalopride is recommended at 2 mg once daily, however the dose for the elderly (> 65 years) and patients with severe renal impairment (glomerular filtration rate < 30 mL/min/m^2) and severe hepatic impairment (Child-Pugh class C) should start at 1 mg once daily. Headache, nausea, abdominal pain, and diarrhoea lead to discontinuation of Prucalopride treatment in approximately 5% of patients. Prucalopride is contraindicated in patients with hypersensitivity, renal impairment requiring dialysis, intestinal perforation or obstruction, and severe inflammatory conditions of the intestinal tract [30]. If treatment with Prucalopride is not effective after 4 weeks, patients should be re-examined and the benefits of continuing treatment should be reconsidered.

Lubiprostone

Lubiprostone is a chloride channel activator and increases intestinal chloride secretion, accelerates transit, and facilitates ease of defecation [30]. Lubiprostone, at 24 μg twice daily, significantly improved stool frequency and consistency, and reduced straining. Lubiprostone was well tolerated and bowel symptoms improved consistently over 48 weeks in adult patients with chronic idiopathic constipation [44-46]. Recently, Lubiprostone produced a steady and effective improvement in the symptoms of chronic constipation with or without IBS in a dose-dependent manner with a good safety profile and tolerability in a Japanese population [47]. The most common adverse event was nausea, and the drug may be associated with diarrhoea, headache, abdominal distention, abdominal pain, flatulence, and vomiting. Lubiprostone may be considered for normal transit constipation or slow transit constipation patients refractory to simple laxatives [12].

Linaclotide

Linaclotide is an agonist of guanylate cyclase C receptors, which stimulates intestinal fluid secretion and transit. In early studies, it has been found to increase bowel movement frequency and loosen stool consistency. Furthermore, abdominal symptoms, global measures of constipation and quality of life were also significantly improved [48,49].

Adverse events are gastrointestinal symptoms (diarrhoea, abdominal pain, flatulence, and abdominal bloating) and headache. Diarrhoea occurred in 20% and only 5% of these abandoned the treatment for this reason. It tends to appear in the first week of treatment, is dose dependent, and remits a few days after discontinuing the drug. In countries where doses lower than 290 μg are not approved and marketed, taking it every other day represents an option to reduce diarrhoea [50-52].

Elobixibat

The bile acid transporter inhibitor. Almost all luminal bile acid is physiologically reabsorbed thorough bile acid transporters of ileal enterocyte. If the reabsorption of bile is blocked by ileal diseases or drugs, the remnant colonic luminal bile acid causes water secretion and facilitates bowel movement. Pharmacodynamic studies showed that bile acid transporter inhibitors accelerate colonic transit and relieve constipation related symptoms [53,54]. Although Eloxibibat is a generally well-tolerated drug, abdominal pain may be present in 36 - 50% of those who receive it, causing treatment to be abandoned in 25% of cases for this reason. Diarrhoea is also a frequent adverse effect, present in around 12% of those being treated [55].

Enemas and Suppositories

An enema is a popular method of treatment for constipation and has been used for hundreds of years in a variety of forms, including water, soapsuds, phosphate, and sugar solutions. By distending the rectum, all enemas stimulate the colon to contract and eliminate the stool.

Sodium phosphate enemas osmotically increase stool content and volume facilitates bowel movements in 5 to 10 minutes. Therefore its absorption is minimal. When retention time of the enema increases there is a risk of increased passage of liquid to the colon, with ensuing dehydration, and the absorption of phosphate and sodium causing hypernatremia and hyperphosphatemia [56].

Suppositories can help to initiate or facilitate rectal evacuation and have been used for many decades. Glycerine suppositories are assumed to stimulate rectal contractions through mucosal irritation and dehydration [14]. Bisacodyl is supposed to stimulate the rectum directly.

Conclusion

All the medications currently available for the treatment of functional constipation are superior to its placebos, with an appropriate safety profile when used at established doses under medical supervision. However, there are no direct comparisons between different drug classes to help with treatment algorithms. Head to head trials of active agents are necessary to determine the optimal selection of pharmacological agents for functional constipation.

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