Medical Treatment of Constipation

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ABSTRACT

Various agents are used for the medical management of chronic constipation, but few of these have been adequately studied. This article specifically examines the medical treatment of chronic constipation and the available data concerning bulk agents, lubricating agents, stimulants, and osmotic laxatives, used alone and in combination. Most experts consider dietary fiber or medicinal bulk agents to be the initial therapeutic option for the treatment of chronic constipation. If fiber is not successful or poorly tolerated, subsequent treatments may include saline osmotic laxatives, lactulose, 5-hydroxytryptamine₄ (5-HT₄) agonists (tegaserod), or stimulants such as senna or bisacodyl. Recent data also demonstrate both polyethylene glycol laxative and tegaserod to be safe and effective as initial therapy for chronic constipation.

KEYWORDS: Constipation, laxatives, fiber, osmotic agents, polyethylene glycol, 5-HT₄ agonists

Objectives: Upon completion of this article, the reader should be able to summarize the treatment options in the management of chronic constipation.

Although there are many remedies and treatments available for the symptomatic improvement of constipation, only tegaserod (Zelnorm, Novartis Pharmaceuticals, East Hanover, NJ) is approved by the United States Food and Drug Administration (FDA) for the chronic treatment of chronic constipation for individuals younger than 65. All other currently available agents are indicated only for short-term use in “occasional” constipation.¹ Although few agents have been carefully studied, even fewer have been adequately studied in the arena of chronic constipation. Initial management of patients with chronic constipation should include education of the patient, dietary evaluation, and consideration of medical options. Education of the patient is critical and should include explanation of normal physiologic bowel patterns. The focus of this

review is on available therapeutic options utilizing lifestyle modifications, medications, and biofeedback.

LIFESTYLE MODIFICATIONS

Following education and the initial assessment, patients should be encouraged to recognize and respond to the “call to defecate.” Although modest exercise is clearly of benefit for several reasons, increases in physical activity and fluid intake appear not to relieve chronic constipation except in situations of dehydration.^{2,3} Patients may be encouraged to monitor their bowel habits by using a diary to record bowel movements, stool characteristics, and associated abdominal symptoms. Such diaries can be useful when assessing responses to treatment interventions.

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Table 1 Laxatives*Bulk Laxatives*

Dietary fiber, psyllium, polycarbophil, methylcellulose, carboxymethylcellulose

Osmotic Agents

Saline laxatives: Magnesium, sulfate, potassium, and phosphate salts

Poorly absorbed sugars: Lactulose, sorbitol, mannitol, lactose, glycerin suppositories

Polyethylene glycol (PEG): PEG 3350 laxative

Stimulant Laxatives

Surface-active agents: Docusate, bile salts

Diphenylmethane derivatives: Phenolphthalein, bisacodyl, sodium picosulfate

Ricinoleic acid: Castor oil

Antraquinones: Senna, cascara sagrada, aloe, rhubarb

Lubricating Agent

Mineral oil

Neuromuscular Agents

5-HT₄ agonists: Cisapride, norcisapride, prucalopride, tegaserod

Colchicine

Prostaglandin agent: Misoprostol

Cholinergic agents: Bethanechol, neostigmine

Opiate antagonists: Naloxone, naltrexone

Investigational Agents

Recombinant methionyl human brain-derived neurotrophic factor (r-methHuBDNF), neurotrophin-3

Table 2 Treatment Algorithm for Chronic Constipation*Initial Options*

Fiber

Magnesium hydroxide

Polyethylene glycol (PEG) 3350

Tegaserod

Severe Infrequent or Acute Constipation

PEG 3350

Saline laxative (magnesium hydroxide)

Bisacodyl

Senna

Tegaserod

Severe Idiopathic Constipation

Larger doses of osmotic laxatives (saline or PEG)

Lactulose

Neuromuscular drugs (tegaserod)

Combination therapy

Outlet Obstruction

Liquefy stool with osmotic laxatives

Enemas

Pregnancy

Fiber and bulk laxatives

PEG

Lactulose

Bisacodyl

LAXATIVES

With so many potential options available, the choice of initial laxative is subject to much personal opinion and consensus.^{4,5} There are also conflicting opinions about the initial approach to diagnosis before treatment. A useful classification is presented in Table 1. Algorithmic treatment approaches have been developed on the basis of whether constipation is "slow transit" or "normal transit."⁵ Because response to biofeedback is inconsistent⁵ and typical initial algorithms are similar regardless of transit status, laxative therapy can be initiated before additional diagnostic evaluation. Most empirical regimens begin with fiber (Table 2).

SELECTED LAXATIVE OPTIONS**Bulk Laxatives**

The average American diet contains relatively low levels of fiber, and many consider this to contribute to the high prevalence of chronic constipation in the United States. There is a clear dose response between daily fiber intake and fecal output.⁶ Increased fluid intake enhances the effect provided by the increased fiber intake.⁷ Although it is not indicated in patients with pelvic floor dysfunction or anal outlet obstruction, patients with normal or

slow transit constipation should increase their fiber intake to 20 to 35 g daily. Many types of insoluble fiber, such as bran, may cause significant amounts of abdominal bloating and discomfort. It is possible, however, to minimize these symptoms by starting with low doses and increasing amounts over time. Bulk-forming laxatives such as methylcellulose, calcium polycarbophil, and psyllium seed are polysaccharides or cellulose derivatives that absorb water into the colonic lumen and increase fecal mass.⁸ This, in turn, stimulates motility and reduces colon transit time.⁸ Psyllium, a naturally occurring agent, has been demonstrated to delay gastric emptying and depress appetite in some patients.⁸ In addition, esophageal and intestinal obstruction and asthmatic reactions from psyllium have been reported.⁹ Methylcellulose¹⁰ and calcium polycarbophil¹¹ are synthetic fiber polymers that are metabolically inert and resistant to bacterial fermentation.

In patients unresponsive to bulk agents alone, the addition of other laxatives is often the next logical choice. Laxatives come in many forms, each having its own mechanism of action. The particular laxative chosen should be based on both the symptoms experienced and the patient's preferences. Stool softeners such as docusate sodium lower the surface tension of stool, facilitating the passage of water into the stool. There

is, however, little evidence to support their use in chronic constipation.

Osmotic Agents

SALINE AGENTS

Saline laxatives are poorly absorbed or nonabsorbed osmotic preparations that result in the secretion of water in the intestines to maintain isotonicity with plasma.¹² The choice of which saline laxative (magnesium hydroxide, magnesium sulfate, magnesium citrate, sodium phosphate, sodium sulfate) is largely arbitrary.⁴ In patients with either cardiac or renal dysfunction, excessive absorption of sodium, phosphorus, or magnesium may lead to electrolyte and volume overload, and if the laxative is overused, dehydration may occur.¹² For the most part, however, even when these laxatives are ingested as hypertonic solutions, the hypertonicity does not persist, as there is rapid osmotic equilibration.⁸ Electrolytes are not absorbed and an osmotic gap between stool and plasma forms, reflecting the unmeasured substances in stool water. Although the laxative action of magnesium is thought to be due to a local effect in the intestinal tract, it is also possible that released hormones such as cholecystokinin¹³ or activation of constitutive nitric oxide synthase¹⁴ may contribute to this pharmacological effect. Oral phosphates, given in large doses for bowel preparation, can have biochemical side effects of hyperphosphatemia and hypocalcemia.¹⁵ The oral phosphate products are not recommended for use in patients with renal failure or cardiac insufficiency. Sodium sulfate is an effective component of some gut lavage solutions for colon cleansing prior to diagnostic and surgical procedures,¹⁶ but significant absorption may occur in the jejunum.

POORLY ABSORBED SUGARS

Lactulose, a poorly absorbed sugar, is a galactose-fructose disaccharide. As humans lack an intestinal fructosidase, the unabsorbed carbohydrate becomes a substrate for colonic bacterial fermentation with resultant production of hydrogen, methane, carbon dioxide, water, acid, and short-chain or volatile fatty acids.¹ These products act as osmotic agents but also stimulate intestinal motility and secretion. Lactulose increases stool frequency in chronically constipated patients¹⁷ and is best suited for gentle catharsis. Abdominal bloating, discomfort, and flatulence often result from its use and may decrease patients' acceptance. Sorbitol and mannitol, poorly absorbed sugar alcohols, may produce effects similar to those of lactulose if taken in sufficient dosages. Glycerin also has osmotic effects, but its significant absorption in the small bowel prevents its regular use for the treatment of chronic constipation. Some patients who are lactose maldigestors simply adjust their

consumption of lactose-containing foods to regulate their bowel habits.

POLYETHYLENE GLYCOL

High-molecular-weight polyethylene glycol (PEG) is a large polymer with substantial osmotic activity that obligates intraluminal water.¹⁸ PEG is used with balanced electrolytes in solutions for colon cleansing as polyethylene glycol electrolyte lavage solution (PEG-ELS) and sulfate-free electrolyte lavage solution (SF-ELS).¹ These solutions have been shown to be safe and effective for preparation for colonoscopy, barium x-ray examinations, and colon surgery.¹⁶ PEG-ELS and SF-ELS reach a steady-state equilibrium when given in large volumes at high infusion rates (1.5 L/hr) and pass through the gastrointestinal tract with no net water or electrolyte absorption or secretion.¹ However, this is not necessarily the case when they are given in small amounts or ingested at slow rates.

PEG 3350 laxative (MiraLax, Braintree Laboratories, Braintree, MA) is a chemically inert polymer composed of PEG 3350 that does not contain any salt that can be absorbed. DiPalma and colleagues presented data confirming efficacy of MiraLax in a placebo-controlled, randomized, multicenter, parallel-group trial that compared 17 g of PEG 3350 laxative with a dextrose placebo.¹⁹ The greatest efficacy for PEG 3350 was noted during the second week of therapy,¹⁹ but higher doses have been used successfully for the overnight treatment of constipation.²⁰ In this overnight efficacy study, 24 constipated adults were randomly assigned to receive either placebo or a single dose of 51, 68, or 85 g of PEG 3350. The 68-g dose provided the most reliable and safe relief within 24 hours.²⁰ There were no adverse effects and no incontinence, cramps, or diarrhea with any of the doses. There were no changes in measured electrolytes, calcium, glucose, blood, urea, nitrogen (BUN), creatinine, or serum osmolality.

Stimulant Laxatives

Stimulant laxatives, such as bisacodyl and senna, exert their primary effects through alteration of electrolyte transport by the intestinal mucosa⁸ and generally work within several hours. In his classification, Schiller refers to this class of drugs as "secretagogues and agents with direct effects on epithelial, nerve, or smooth muscle cells."⁸ Following their use, it is not uncommon for patients to report symptoms of abdominal discomfort and cramping.²¹ This grouping includes surface-active agents, diphenylmethane derivatives, ricinoleic acid, and anthraquinones (Table 1). Although stimulant laxatives may be associated with occasional side effects such as salt overload, hypokalemia, and protein-losing enteropathy, data do not support the theory that they cause a so-called cathartic colon.²² Melanosis coli, a pigmentation of the

colonic mucosa caused by the accumulation of apoptotic epithelial cells phagocytosed by macrophages, may develop in patients who chronically ingest anthraquinone-containing stimulant laxatives.²³ Despite prior theories to the contrary, neither anthranoid laxative use nor macroscopic or microscopic melanosis coli is associated with any significant risk for the development of colorectal adenoma or carcinoma.²⁴ Phenolphthalein, no longer marketed in the United States, has been associated with fixed-drug eruption, protein-losing enteropathy, Stevens-Johnson syndrome, and lupus reactions.⁸ Castor oil, containing ricinoleic acid, alters intestinal water absorption and motor function,⁸ and side effects often include cramping and nutrient malabsorption.²⁵

Lubricating Agents

Mineral oil is not chemically altered in the body but emulsifies into the stool mass, coating the rectum and providing lubrication.⁸ Side effects include lipid pneumonia (resulting from aspiration), malabsorption of fat-soluble vitamins, foreign-body reactions in tissue, and anal seepage.

5-HT₄ Agonists

Tegaserod, a partial peripheral 5-hydroxytryptamine₄ (5-HT₄) receptor agonist, is approved by the FDA for the treatment of irritable bowel syndrome with constipation and has proved relatively safe in numerous trials.^{26,27} It has also been approved by the FDA for the treatment of chronic constipation in both men and women younger than 65. By agonizing 5-HT₄ receptors, tegaserod probably acts by enhancing the peristaltic reflex. Although it was designed to mimic serotonin, chemical alteration decreases its peripheral effect by enhancing passage through the blood-brain barrier.²⁸ Several reports of intestinal ischemia have been noted in postmarketing reports, leading to changes in product labeling. Health care providers are advised to evaluate quickly patients receiving tegaserod who present with worsening diarrhea or symptoms suggestive of intestinal ischemia, including abdominal pain or rectal bleeding.

LAXATIVE USE IN SPECIAL CIRCUMSTANCES

Children

The treatment options for children are similar to the options for adults.²⁹ Although constipation is a common problem, there are few clear treatment guidelines with evidence-based analysis.³⁰ Recent data concerning PEG 3350 laxative show safety, efficacy, and preference by children and parents in studies of short- and long-term use in comparison with agents such as milk of magnesia

and lactulose.^{31–33} PEG 3350 laxative is not yet approved by the FDA for use in children.

Although constipation in adults and children is a chronic condition that warrants chronic therapy, no agent has approval for chronic use. Therefore, guidelines reviewed here describe off-label use. There are data to support chronic PEG use in children,³³ and studies are in progress evaluating the chronic use of PEG in adults.

Pregnancy

Most obstetricians advise avoiding laxatives in pregnancy and prescribe stool softeners instead. Dietary fiber and bulk laxatives such as psyllium, methylcellulose, and polycarbophil are most physiologic and safest during pregnancy.³⁴ Stimulant laxatives can be used but are reserved for those who do not respond to these initial measures. PEG, lactulose, sorbitol, glycerin, bisacodyl, and senna have been cited as being preferred.³³ Safety is not established for PEG 3350 laxative (FDA Pregnancy Category C), but PEG is chemically inert, with minuscule absorption, and toxicity has been thought to be unlikely.³³ A consensus panel felt that PEG laxative met the criteria for the ideal treatment for pregnancy constipation.³⁵ Tegaserod is Pregnancy Category B. Misoprostol (Pregnancy Category X) and colchicine (Pregnancy Category D) should not be used in pregnancy.

Castor oil should be avoided during pregnancy because of the possibility of stimulating premature uterine contractions. The saline osmotic laxatives, such as magnesium salts and monobasic and dibasic sodium phosphate (Phospho-Soda), should also be avoided because of unwanted sodium and water retention.³⁴

Nardulli and colleagues evaluated PEG for constipation in the puerperium, randomly assigning 225 subjects in a prospective, open-label trial,³⁶ and found PEG to be effective and without side effects.

KEY POINTS

- Few agents have been carefully studied for the treatment of constipation, particularly for chronic use.
- Only tegaserod has FDA approval for the chronic treatment of chronic constipation.
- In general, there are few data indicating that lifestyle changes or exercise significantly affects constipation symptoms.
- Dietary and medicinal fibers and synthetic polymers share the property of holding water in the stool. The increased intraluminal volume stimulates motility, increases stool weight, and reduces colon transit time.
- Stimulant laxatives have been so called because of the belief that they stimulate motility. They actually have effects on mucosal transport and motility.

- Salts of magnesium and poorly absorbed anions, such as sulfate or phosphate, obligate water excretion into the intestinal lumen.
- Tegaserod and polyethylene glycol laxative are acceptable initial agents.

DISCLOSURE

Dr. Di Palma serves as a consultant to Braintree Laboratories and Novartis Pharmaceuticals.

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