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Use of macrogol 4000 in chronic constipation

R. DE GIORGIO[1], R. CESTARI[2], R. CORINALDESI[1], V. STANGHELLINI[1], G. BARBARA[1], C. FELICANI[1], G. DI NARDO[3], S. CUCCHIARA[3]

[1]Department of Clinical Medicine, School of Medicine, Alma Mater Studiorum University, Bologna (Italy)
[2]Digestive Endoscopy, Department of General Surgery, School of Medicine, University of Brescia – Spedali Civili, Brescia (Italy)
[3]Department of Pediatrics, School of Medicine, University "La Sapienza", Rome (Italy)

Abstract. – *Background:* **Chronic constipation is a common functional disorder of the gastrointestinal tract, affecting up to 35% of the general population, and especially the elderly. However, its definition as perceived by the patient can vary, making it difficult to understand the problem and find appropriate therapeutic measures. The approach to chronic constipation, thus, needs a thorough understanding of the patient's complaint and the main pathophysiological mechanism requiring treatment. Lifestyle changes do not usually meet with complete patient satisfaction. Other treatments include different types of laxatives. Of these, osmotic laxatives appear one of the most effective and are, therefore, frequently prescribed.**

Design: **This review will cover the topic of osmotic laxatives, specifically focusing on polyethylene glycol (PEG/macrogol 4000) in chronic constipation and as a key agent for bowel cleansing prior to colonoscopy. PEG formulations, including macrogol 4000, are safe, effective treatments for constipation, even in children and elderly patients. Macrogol 4000 may well be more palatable than combined formulations (macrogol 3350 with electrolytes), which could help improve adherence to the long-term treatment required for chronic constipation.**

Conclusions: **PEG/macrogol is also recommended as an effective option for bowel cleansing prior to colonoscopy. The improved cost-effectiveness of macrogol over other commonly prescribed laxatives, such as lactulose, should be taken into consideration.**

Key Words:

Chronic constipation, Polyethylene glycol, Osmotic laxatives, Colonoscopy

Introduction

Chronic constipation is a functional disorder of the gastrointestinal tract characterized by dry feces and difficult, infrequent evacuations in the absence of detectable abnormalities. This condition is very common in the general population, with a prevalence ranging from 2% to 35%. Females (female-to-male ratio of 2-3:1), the elderly (>65 years of age), people of non-European descent and those with a lower socioeconomic status are more likely to be affected[1,2]. Only a fraction (approximately 25%) of patients consults a doctor, while most seek alternative solutions such as the advice of pharmacists or practitioners of herbal medicine. As with other functional bowel diseases (e.g. irritable bowel syndrome and dyspepsia), the quality of life of patients with chronic constipation can suffer as much as patients with organic diseases such as chronic obstructive pulmonary disease or diabetes[3,4].

There is no consensus on the definition of constipation, making it difficult to understand the problem and find appropriate therapeutic measures. The classic criterion used by some patients is a limited number of evacuations per week[5], while others consider themselves constipated if they have hard stools or must strain excessively during defecation. Although epidemiological studies confirm that 2-3% of the population have few (less than three) bowel movements per week, this number is only an approximate criterion for defining constipation and may cause the real number of affected patients to be underestimated considerably. International groups of experts have, thus, developed symptom-based criteria (the best known of which being the Rome criteria) for an appropriate definition.

According to the most recently accepted Rome III criteria[2], a patient is defined as constipated if he or she has suffered two or more of the following symptoms for at least 3 months with symptom onset at least 6 months prior to diagnosis:

Corresponding Author: Roberto De Giorgio, MD, Ph.D.; e-mail: roberto.degiorgio@unibo.it

- Straining during at least 25% of defecations;
- Lumpy or hard ("nut-like") stools in at least 25% of defecations;
- Sensation of incomplete evacuation for at least 25% of defecations;
- Sensation of anorectal obstruction for at least 25% of defecations;
- Manual maneuvers to facilitate defecation in at least 25% of defecations;
- Fewer than 3 defecations/week;
- Loose stools rarely present without use of laxatives;
- Insufficient criteria to justify a diagnosis of irritable bowel syndrome (IBS).

Chronic constipation may be associated with a further degree of disability, if patients have impacted feces in the rectum or in more proximal segments of the colon. This may lead to paradoxical diarrhea ("overflow") or incontinence ("soiling"), which further worsens the patient's quality of life[1-3].

Diagnostic Approach

In most patients constipation is an expression of an underlying abnormal colorectal function that is not associated with organic (inflammatory, neoplastic) disorders of the gastrointestinal tract. Nonetheless, it should be stressed that at least in a minority of patients, constipation may be the first alarm symptom of disease, such as cancer, or a symptom of metabolic abnormalities (e.g. hypothyroidism or hypercalcemia) or neurological diseases (e.g. Parkinson's disease) (Table I)[6]. Figure 1 illustrates a simple diagnostic algorithm with different tests which can be applied to better standardize the approach to patients with chronic constipation.

A thorough history taking and clinical evaluation are extremely important in order to rule out any organic or systemic disease. It is useful to evaluate the clinical presentation of the illness (chronic vs. recent constipation), drug use, with special attention to medicines capable of slowing down gastrointestinal motility and transit (such as opiates, analgesics, tricyclic antidepressants, diuretics, calcium channel blockers, nitrates, antihistamines, anti-psychotic and antiparkinsonian agents – see also Table I), alarm signs and symptoms (e.g. weight loss, rectal bleeding, palpable abdominal masses, increased erythrocyte sedimentation rate), and the coexistence of neurological illnesses. Perineal inspection and rectal examination are essential to exclude the presence of anal fissures, fistulas, abscesses or neoplasms. Further examinations, including a complete

Table I. Causes of chronic constipation.

Mechanical
- Stenosing neoplasms
- Extrinsic compression (e.g. pelvic tumors)
- Painful hypertonicity of the anal canal (idiopathic anal fissure)
- Stenosis/fibrosis of the anal canal

Pharmacological
- Anticholinergics
- Antihistamines
- Calcium-channel blockers
- NSAIDs
- Dopaminergics
- Tricylic antidepressants
- Antipsychotics
- Opiates
- Iron therapy
- Aluminum salts (antacids)
- Cholestyramine
- Diuretics
- Antidiarrheals

Surgical
- Abdominal–pelvic surgery (adhesions)
- Colon surgery (anastomosis of insufficient size)
- Anorectal surgery (postoperative stenosis)

Endocrine
- Hypothyroidism
- Pheochromocytoma
- Addison's disease

Neurological and Psychiatric
- Hirschsprung's disease
- Diabetic neuropathy
- Multiple sclerosis
- Parkinson's disease
- Autonomic neuropathies
- Guillain-Barre Syndrome
- Spinal lesions
- Damage to the sacral parasympathetic nerves
- Anorexia nervosa
- Depression
- Dementia

Pregnancy

Dehydration

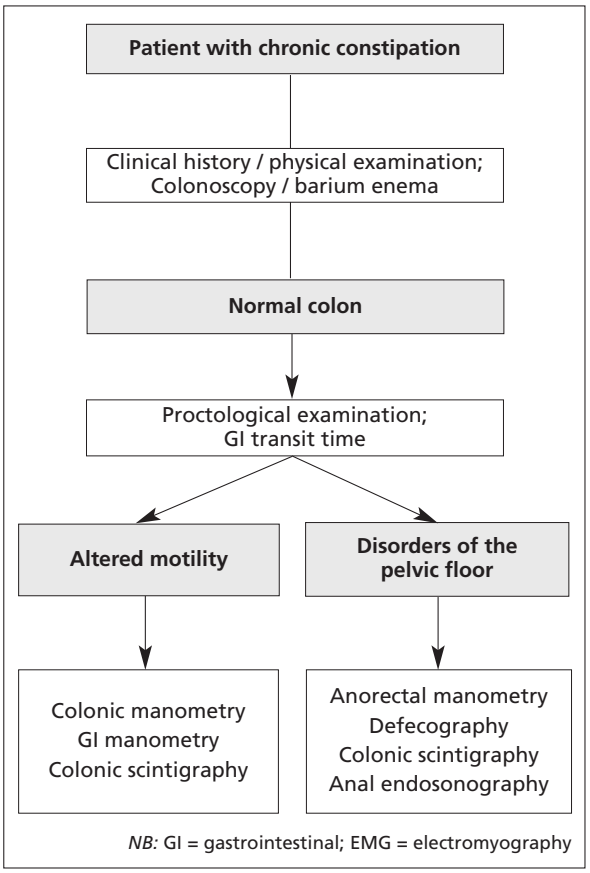

Figure 1. Diagnostic algorithm of chronic constipation.

blood screening along with radiological (double contrast barium enema) and endoscopic (colonoscopy) examinations, are advisable in selected cases, based on clinical history and presence of alarm signs/symptoms. Functional tests aimed at assessing intestinal motility/transit and anorectal impairment may be useful to establish the mechanisms underlying idiopathic chronic constipation and tailor appropriate therapeutic options[1,6].

Main Pathophysiological Mechanisms

In the absence of reliable biomarkers, chronic constipation is considered a functional bowel disorder to which different mechanisms contribute. From a pathophysiological standpoint, there are three main subtypes:

1. Normal transit ("functional constipation");
2. Slow transit;
3. "Obstructed" defecation (or dyssynergic defecation when purely functional).

The relative impact of each of these forms is approximately 59%, 13% and 25% of cases[7,8]. Patients with overlapping slow transit and obstructed defecation may also be observed in the clinical setting.

Irritable bowel syndrome with constipation (IBS-C) is a common condition in which chronic or recurrent constipation is associated with normal gut transit. IBS-C can be differentiated from normal transit constipation by the presence of abdominal pain, predominant in IBS with respect to functional constipation[2,9].

In this short review, we will focus on the two major forms of constipation, slow transit and obstructed defecation. Colonic motor activity is mainly under the control of the enteric nervous system, while defecation is the result of pelvic reflexes and voluntary control[6]. Before looking at the pathophysiology, it is important to point out that colonic motor activity is mainly irregular, increasing after meals and upon awakening and decreasing during sleep. Colonic motility generally consists of non-propagated waves which facilitate the mixing of endoluminal contents in order to maximize water and electrolyte absorption. Propulsive waves include low- and high-amplitude propagated contractions (LAPCs and HAPCs, respectively)[6,7,9]. HAPCs are capable of rapid movement of the endoluminal contents and often precede defecation. Patients with chronic constipation have a significantly reduced number of HAPCs (<5/day) compared to non-constipated subjects[6,7,9]. Furthermore, the so-called gastrocolonic reflex, which exerts an important control on colonic peristalsis, is reduced in patients with chronic constipation[11]. Taken together, these findings support the concept that impaired colonic motility has an important role in delaying transit in a subset of patients with chronic constipation (i.e. those with slow transit [or *propulsive*] constipation). This type may occur in the absence of major systemic or gastrointestinal disorders, although it can also be associated with neurological impairment (e.g. supraspinal causes, spinal lesions, diseases of the autonomic nervous system, whether extrinsic or intrinsic – the latter is also referred to as the enteric nervous system, or the "brain-in-the-gut", due to its independence from the central nervous system in controlling virtually all gut functions) or with endocrine and metabolic disorders (hypothyroidism, hypercalcemia, porphyria, diabetes mellitus)[6-10].

The total intestinal transit time can be evaluated by giving the patient radiopaque markers oral-

ly and assessing their location along the alimentary tract by direct standard abdominal radiography. On average, in normal subjects 80% of markers are evacuated within 4 days. In patients with slow transit constipation, expulsion is reduced, and the markers will be distributed through the different segments of the colon[11].

Obstructed defecation is caused by a pelvic floor disorder. This condition is also referred to as dyssynergic defecation when it is purely functional and not associated with hemorrhoids, genital prolapse, anismus (paradoxical contraction of the pubo-rectalis muscle), solitary rectal ulcer syndrome, idiopathic perineal pain syndrome, or anterior or complete rectal mucosal prolapse. It is caused by either paradoxical contraction/inadequate relaxation of the pelvic floor muscle or inadequate propulsion during defecation. Diagnostic examinations such as anorectal manometry (which assesses internal anal sphincter relaxation following rectal distension), rectal balloon expulsion test, defecography (videoradiographic recording of defecation using a contrast medium in the rectum), and electromyography of the anal muscles and pelvic floor can be useful to determine the type and degree of dysfunction in patients with obstructed/dyssynergic defecation[12]. The challenge for clinicians dealing with patients with chronic constipation is to appreciate the nature of the patient's complaint, understand the predominant underlying pathophysiological mechanism (slow transit vs. obstructed /dyssynergic defecation), and select treatment strategies to improve symptoms and quality of life.

Treatment

Patients with chronic constipation often self-medicate by changing their diet (increased dietary fiber intake) and, above all, using irritant laxatives. In the United States, about $400 million is spent on over-the-counter laxatives and roughly 5 million medical prescriptions are written for the treatment of constipation every year (8). Nonetheless, around 50% of constipated patients are still dissatisfied with their treatment. Remedies for constipation are generally unsatisfactory because although they may ensure regular bowel movements, they do not always resolve (and may even worsen) the signs and symptoms (e.g. pain and abdominal bloating, flatulence, and straining) which are actually responsible for the negative impact on the patient's quality of life. Tailoring an effective treatment for chronic idiopathic constipation is, thus, a challenge for clinicians[1,6,8].

Non-pharmacologic strategies are the first step and include educating the patient on the physiologic basis of defecation, the role of diet and adequate daily fluid intake, and physical exercise (a sedentary lifestyle causes a threefold increase in the risk of constipation). Patients should also be instructed to attempt defecation in the morning (within two hours of awakening) and following meals, when colonic motor activity is at its highest[1,6,8].

Increased dietary fiber (20-30 g/day) is known to reduce colonic transit time. However, not all patients will respond to this treatment and it may even exacerbate the symptoms of some (patients with slow transit constipation). It is, thus, important to establish the predominant form of the constipation and the underlying pathophysiologic mechanism before suggesting dietary fiber supplementation to any patient[1,6,8].

In addition to lifestyle changes, which, as noted, are not always fully effective, different types of laxatives can be prescribed by doctors. Laxatives are agents that stimulate defecation or modify stool consistency and ease of passage. Although they are generally recommended for short-term treatment, current evidence suggests that they are the first-line remedy for constipation[13,14]. There are at least three major categories of laxatives based on their mechanism of action (Table II): bulk-forming, osmotic and stimulants (also referred to as "irritants"). In some countries (e.g. United States), a fourth category is available, i.e. stool softeners, such as docusate[13,14].

In this review, we will focus on osmotic laxatives, and particularly polyethylene glycol (PEG, also referred as macrogol). This compound has

Table II. Classification of major laxatives based on mechanisms of action.

Bulk-forming agents
- Psyllium
- Methylcellulose

Osmotic agents
- Poorly absorbable disaccharides (lactulose)
- Polyethylene glycol 3350/4000
- Poorly absorbed ions (magnesium hydroxide)

Stimulant laxatives
- Diphenylmethane derivatives (Bisacodyl)
- Anthraquinones (cascara, senna, frangula)

Stool softeners
- Docusate

gained grade A recommendation for the treatment of chronic constipation in different studies and meta-analyses[14-16]. We will examine the clinical efficacy of PEG/macrogol in chronic constipation and as a key agent for bowel cleansing before colonoscopy.

Osmotic laxatives are normally small ions (e.g. magnesium sulfate or phosphate salts) which exert their osmotic effect in proportion to the number of molecules present in the intestinal lumen. Large molecules are not normally particularly effective in generating significant osmotic pressure, due to their molecular weight. However, some organic polymers, including PEG/macrogol, are an exception and do have a powerful osmotic effect. The osmotic activity of PEG/macrogol is related to its ability to sequester water in the intestinal lumen. PEG with molecular weights <1500 are absorbed by the intestinal mucosa and are, thus, unsuitable as osmotic compounds[17]. In contrast, those with higher molecular weights (e.g. 3350 or 4000) are only minimally absorbed, thereby sequestering water in the bowel. Since PEG/macrogol is an inert molecule which cannot be metabolized by the intestinal microflora, it should be delivered from the small intestine to the colon, where it evokes its osmotic activity[17]. This causes the volume of the fecal mass to increase (due to a higher water content), which in turn triggers propulsive motor processes, such as peristalsis, via distension of the colonic wall. The increased hydration also softens the feces and eases defecation.

There is consistent evidence that a relatively low dose of PEG/macrogol (17 g/day) improves stool frequency and consistency in patients with chronic constipation, as clearly shown in recent meta-analyses[14-16]. In one metanalysis with more stringent criteria for study evaluation, the relative risk ratio in terms of mean number of stools per week in 573 patients (included in 4 eligible studies) was significantly in favor of PEG/macrogol treatment[14]. PEG/macrogol, which is usually effective within 48 hours, improves quality of life even in the elderly, a particular subgroup more prone to severe constipation that is often refractory to various treatment options, including irritant laxatives[18].

There are at least two pharmaceutical formulations of PEG/macrogol, based on its molecular weight: 3350 and 4000. PEG/macrogol 3350 is commonly combined with variable amounts of electrolytes (e.g. sodium sulfate), believed to combat possible electrolyte depletion over time, whereas PEG/macrogol 4000 is generally not combined with electrolytes, making it slightly more palatable than other PEG compounds[16-18]. This is particularly true for constipated children and the elderly, whose adherence to long-term treatment could be improved by using more palatable PEG formulations, such as macrogol 4000, which is tasteless, odorless and can be mixed with different beverages to facilitate its use[16,19,20]. PEG/macrogol 4000 does not cause fluid or electrolyte imbalance even in prolonged treatment[18-20]. Moreover, like other PEG formulations it does not induce tolerance, as it continues to be effective in the long term, without necessitating dose increase over time. There is no clear difference in the efficacy of various PEG/macrogol formulations. In a study comparing the efficacy of PEG/macrogol with and without electrolytes in constipated patients, both PEG formulations were well tolerated and equally effective in improving bowel frequency at any of the doses tested[21].

PEG/macrogol treatment is usually safe and not associated with severe side effects. However, diarrhea and bloating may be experienced by a subset of patients. Bloating may result from faster transit, occurring when large doses of PEG/macrogol are administered after meals. In these circumstances, nutrients enter the colon and activate fermentation, producing excessive gas. This problem can be alleviated by taking PEG/macrogol before going to bed.

Finally, in comparison with other laxatives, especially irritants (anthraquinones), PEG/macrogol does not alter the normal morphology and architecture of the gastrointestinal mucosa, as demonstrated by histological studies[18].

The effective dose of macrogol 4000 ranges from 0.7 to 1.5 g/Kg/day in constipated patients of any age (Table III). When clinically necessary,

Table III. Age-related recommended dosages.

Age	Body weight (Kg)	Daily dose
Children 2-8 years old*	6-9	5 g
	10-12	7.5 g
	13-16	10 g
	17-20	12.5 g
Adults and children > 8 years old	> 20	10-20 g**

*Usual initial dose is 0.7 g/Kg/die. **Never exceed daily maximum dose (20 g of macrogol).

the standard dose may be taken two or three times per day, provided that patients consume sufficient water to avoid removal of fluids from the body. PEG/macrogol treatment may be of most benefit to the elderly[16,18] and children[19,20]. Another group which may benefit is pregnant women, given the need to adhere to strict safety factors for any treatment during pregnancy. In this respect PEG/macrogol 3350 or 4000 should be considered a first-line option, due to its minimal absorption (1-4%) and elimination in the urine without being metabolized[22,23].

PEG/macrogol formulations have proven effective for bowel cleansing before colonoscopy when taken appropriately and under ideal conditions[24-26]. Solutions of PEG/macrogol in water are isotonic and poorly absorbed, and when introduced quickly (>1800 mL/h) they can exert a substantial osmotic effect in the colon, leading to bowel cleansing. This mechanism also prevents major fluid exchange across the colonic mucosa, thus limiting the risk of dehydration or electrolyte depletion. Several studies have indicated that PEG/macrogol is a valid option for colonoscopic preparation. However, its efficacy may be hampered by poor patient adherence, mainly related to the need for a high fluid intake (at least 4 L), which many patients find unpleasant and difficult to tolerate[25]. This is certainly the case for macrogol 3350 with electrolytes; data for macrogol 4000 are not yet available.

Finally, the osmotic properties of PEG/macrogol 4000 (in 1-2 L of water) could be exploited to improve endoscopic investigation, e.g. video capsule endoscopy of the small bowel, as suggested by international guidelines[27]. The purpose would be to enhance bowel loop distension in order to optimize resolution. Using the same principle, PEG/macrogol has already been used to improve assessment of the bowel wall during ultrasound scans[28].

In conclusion, the evidence to date indicates that like other PEG formulations, macrogol 4000 is a safe, effective treatment for chronic constipation in any age group[9]. It is more palatable than combined formulations (macrogol 3350 incorporating electrolytes), which might help improve adherence to the long-term treatment necessary for patients with chronic constipation. The improved cost-effectiveness of macrogol over other commonly prescribed laxatives such as lactulose, as demonstrated by a recent meta-analysis[15], should also be taken into consideration.

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