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Constipation Treatment in Neurological Disorders

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1. Introduction

Bowel dysfunction is common in patients with neurological diseases. Its prevalence ranges from 30% to 60% in patients with cerebrovascular diseases and new-onset constipation occurs in 55% of patients after a stroke (Su et al., 2009; Harari et al., 2004; Robain et al., 2002; Bracci et al., 2007). In Multiple Sclerosis (MS) constipation is a frequent bowel symptom and it has been observed in up to 73% of patients (Crayton et al., 2004; Gulick et al., 2011; Wiesel et al., 2000). In Parkinson's disease (PD) constipation is one of the most frequent non-motor features, believed to occur in over 50% of patients (Wood et al., 2010; Pfeiffer et al., 2003; Wolters et al., 2009). Disorders of the anorectal sphincters consist of incontinence or difficulty in expelling faeces. Constipation is almost always associated with slowed bowel transit. It may be due to sphincter incoordination in relation to the detrusor mechanism or to detrusor weakness causing loss of propulsive force (Swash et al., 2001). Constipation may have a significant impact on quality of life and would restrict patient's social activities, increasing levels of anxiety and depression, so that symptoms' management is critically important (Ng et al., 2005). This review describes the possible pathogenesis of constipation in neurological disorders, pharmacological therapies available for constipation and management approaches that may increase the likelihood of satisfactory treatment outcomes.

2. Constipation in stroke

Constipation is defined as two or fewer bowel movements per week, the need to manipulate the rectum digitally to facilitate defecation all or most of the time, and/or use of laxatives, enemas or suppositories more than once a week (Hinds et al., 1990). Medical complications after acute stroke are common, ranging from 28% to 96% (Hong et al., 2008). Bowel dysfunction are the most frequent gastrointestinal complaints with a negative impact on patients' quality of life, restricting their social activities (Bracci et al., 2007; Su et al., 2009). The prevalence of constipation after stroke varies from 30% to 60% (Harari et al., 2004). New-onset constipation is seen in 55% of patients within a month after first stroke, strongly relating to disability. Its development may predict a poor outcome at 12 weeks in patients with moderately severe stroke (Su et al., 2009).

New onset constipation occurs in 30% of hemiplegic patients and has no relationship with the hemispheric side or with the severity of stroke even if a trend of reduced risk of constipation is described in patients with ischemic event and less widespread lesion (Bracci et al., 2007). Risk factors for constipation among stroke patients include use of a number of different drugs, dehydration, older age and immobility (Bracci et al., 2007; Su et al., 2009; Kumar et al., 2010). For the elderly, acute hospitalization is at higher risk to develop constipation than in other age groups (Cardin et al., 2010). The highest risk of new-onset constipation occurs on one week after stroke, so that early intervention may prevent the development of bowel dysfunction (Su et al., 2009). Treatment with nitrates and antithrombotics represents an independent risk factor for developing chronic constipation. Nitrates may cause constipation due to the inhibitory role in gut motility secondary to the release of nitric oxide. Antithrombotic drugs, such as acetyl salicylic acid (ASA), indobufen and ticlopidine, have been reported to be associated with bowel dysfunction. ASA and NSAID are more frequently associated with constipation probably via inhibition of the propulsive activity by preventing the release of prostaglandins. Indobufen and ticlopidine are usually associated with diarrhea. No significant association has been described between new onset constipation and ACE inhibitors or anticoagulants (Bracci et al., 2007). Anticholinergic drugs, such as antipsychotics, tricyclic antidepressants or oxybutynin, significantly increase the risk of faecal incontinence in patients with stroke, decreasing gut motility and causing constipation with overflow incontinence (Kumar et al., 2010). The use of diuretics such as mannitol or furosemide is associated with new-onset constipation (Su et al., 2009).

Bed rest and immobility contribute to constipation onset. Hypovolemia, as a result of dysphagia and/or impaired thirst mechanisms, is another risk factor. Between 37% and 78% of patients with stroke develop dysphagia, with a restriction of oral intake of dietary fibre and a high risk of undernutrition and dehydration (Ullman et al., 1996; Kumar et al., 2010; Su et al., 2009).

It is well known that the central nervous system (CNS) takes part in the control of visceral functions and its damage can lead to gastrointestinal impairment (Bracci et al., 2007). Lesions affecting the pontine defecatory centre may disrupt the sequencing of sympatical and parasympathical components of defecation, and impair the coordination of the peristaltic wave and the relaxation of the pelvic floor and external sphincter (Ullman et al., 1996). Constipation could be a clinical manifestation of spinal cord stroke as a consequence of pelvic autonomic dysfunction (Sakakibara et al., 2008).

3. Constipation in MS

Constipation may represent an early symptom of MS and large bowel impairment can precede the onset of MS by many years (Lawthom et al., 2003; Chellingsworth et al., 2003). Bowel dysfunctions are multifactorial and include neurological impairment, behavioural problems, inappropriate toilet facilities, side effects of drugs or coexistent disorders. A multidisciplinary approach is the best way to deal with this symptom. Bowel symptoms should be carefully treated because sometimes helping constipation can precipitate faecal incontinence. Certain patients would prefer to remain constipated if incontinence is thereby avoided (Wiesel et al., 2001). Gastrointestinal symptoms are common in patients with MS and are much more frequent than in the general population (Wiesel et al., 2001). The

prevalence of constipation, alone or in association with faecal incontinence, ranges between 35% to 73%, depending on definitions and selection (Crayton et al., 2004; Gulick et al., 2011; Wiesel et al., 2000; Bakke et al., 1996). There is no difference between male and female patients regarding constipation frequency that presents a strong correlation with disability and disease duration (Hinds et al., 1990). Bladder and bowel dysfunctions have a significant role in psychosocial disability of MS patients, affecting quality of life (Wiesel et al., 2001).

Pathophysiology of constipation in MS is poorly understood. Central nervous system lesions, related to the disease process, may be responsible in some cases, affecting the extrinsic neurological control of gut and sphincter function. Autonomic nervous system impairment, specifically involving parasympathetic pathways, or some systemic mechanism not well known, similar to that which causes fatigue in MS, have been proposed (Fowler et al., 1997; De Seze et al., 2001; Guinet et al., 2011). Some authors have suggested a cerebral involvement or a motor spinal pathways failure as a cause of constipation in MS (Haldeman et al., 1982; Mathers et al., 1990). Abnormalities of colonic activity and prolonged colonic transit time have been demonstrated in some patients, and difficult defecation due to failure to relax the pelvic floor muscles has been found in others (Mark et al., 1999). Whether pelvic floor incoordination shown in some patients with MS should be regarded as a behavioural phenomenon, as in non-neurological constipation, or as related to the MS is yet unknown (Wiesel et al., 2000). Some authors associated large bowel dysfunction to demyelinating lesions of the conus medullaris, even if the role of more proximal lesions cannot be ruled out (Taylor et al., 1984). Other features connected to MS, compromising pelvic floor function and visceral motility, may contribute to constipation: muscle weakness, fatigue, spasticity and poor mobility. Also some medications, commonly used to manage different MS symptoms, such as anticholinergics, antidepressants, opiates and muscle relaxants, can affect bowel function (Wiesel et al., 2001; Fowler et al., 1997; Nordenbo et al., 1996; Gill et al., 1994). Finally, psychological factors or behavioural problems may also affect toileting (Wiesel et al., 2000).

4. Constipation in spinal cord injury

Bowel dysfunction is one of the major sequelae of spinal cord injury (SCI), with a severe impact on long-term quality of life, also increasing anxiety and depression. The prevalence of constipation in subjects with SCI is 20-58% (Ng et al., 2005). It is well known that constipation in SCI is due to prolonged colonic transit time. In SCI the extrinsic neural control is lost with an altered sympathic function (Winge et al., 2003). There is a clear association between constipation and the presence of a higher level of injury, as demonstrated by a mouth-to-cecum transit time prolonged in quadriplegics rather than paraplegics (Rajendran et al., 1992). Patients with cauda equina lesions may have an atonic bowel and develop severe and chronic constipation (Winge et al., 2003).

The variation in constipation prevalence in patients with different levels of neurologic deficit are related to different factors, such as attenuated gastrocolonic reflex, weakness of abdominal and perineal musculature, anorectal dysfunction and body immobilization (Stark et al., 1999; Ng et al., 2005).

Treating constipation in SCI subjects can be demanding. The usual management is a combination of bulking agents and scheduled enemas. Bowel training is used to evacuate

the colon at regular intervals and an adequate fiber and fluid intake maintains bowel movements in a soft and bulky form. Shortly after breakfast, a rectal suppository and digital stimulation of the anorectum are used to induce reflex evacuation. These treatments usually leads to a daily planned evacuation. When they fail, prokinetic agents, parasympathetic nerve stimulators or colostomy can be used (Stark et al., 1999). In selected patients, transanal irrigation improves bowel function, compared with conservative management (Christensen et al., 2006).

5. Constipation in Parkinson Diseases (PD)

Bowel dysfunction is the most commonly observed non-motor feature of PD and it is a major factor in determining quality of life, progression of disability and nursing care (Hely et al., 2005). Some authors found constipation in 29% of patients (Edwards et al., 1991). However this symptom is under-recognised and under-treated but it has the potential to be more debilitating than motor features. The reason of this could be the patients' unawareness that these symptoms are linked to PD. Constipation is frequently reported as a prominent complaint before the onset of motor symptoms in about 50% of patients (Wood et al., 2010). Recently, an epidemiological study revealed an association between frequency of bowel movements and the risk of developing PD. Those patients with an initial finding of constipation were at a 3-fold increased risk of developing PD after 10 years from the initial report of constipation (Abbott et al., 2001). Bowel dysfunction can occur across all stages of PD but often occurs earlier during disease course and it might precede motor symptoms onset by more than a decade, correlating closely with the progression of Lewy pathology (Korczyn et al., 1990; Chaudhuri et al., 2009).

Bowel dysfunction can consist of both slowed colonic transit with consequent reduced bowel-movement frequency and difficulty with the act of defecation itself with excessive straining and incomplete emptying (anorectal dysfunction). Anorectal dysfunction is the more prevalent form of bowel impairment in PD Recognition can lead to earlier and potentially more effective therapeutic intervention (Pfeiffer et al., 2003).

An efficient and successful defecation requires the coordinated contraction and relaxation of several muscles. Defecography, anorectal manometry and analsphincter electromyography have been used to study defecation in PD, showing different abnormalities (Stocchi 2000). In a group of patients, anorectal dysfunction caused a paradoxical contraction of voluntary sphincters during defecation, which is believed to be a type of focal dystonia (Mathers et al., 1989).

Control of gastrointestinal function is complex and involves components of the central, autonomic, and enteric nervous systems (Pfeiffer et al., 2003). Changes in parasympathetic autonomic supply to the gut could certainly account for the impairment of gastrointestinal function in PD but abnormalities in the enteric nervous system within the gut itself have also been identified, including both Lewy-body formation and loss of dopaminergic neurons (Pfeiffer et al., 2003).

Lewy body pathology in the myenteric plexus, leading to colonic sympathetic denervation, has long been recognized in patients with PD. Such pathologic changes are associated with prolonged intestinal transit time and constipation, symptoms believed to occur in ~80% of patients with PD (Jost et al., 1997). Recently, Politis et al. have suggested a dopaminergic

contribution to several non-motor symptoms of PD, including autonomic dysfunction and constipation (Politis et al., 2008).

Apomorphine treatment can improve anorectal dysfunction in PD and suggests that abnormalities of defaecation and anorectal function could be a consequence of dopamine deficiency secondary to the pathological changes of PD (Chaudhuri et al., 2009).

Medications used to treat the motor symptoms of PD (levodopa, anticholinergics) have even been implicated in further slowing of gastrointestinal motility and exacerbation of gastrointestinal dysfunction (Wood et al., 2010).

6. Assessment of constipation

A carefully taken history, including ongoing drugs and physical examination may be adequate in most cases. To perform more specific tests depend on single cases. It is possible to evaluate different aspects of bowel dysfunction. Measurement of whole gut transit time, swallowing a radio-opaque contrast medium, is the most widely used, non-invasive and inexpensive method to quantify large bowel function (Gill et al., 1994; Prokesch et al., 1999; Nicoletti et al., 1992; Evans et al., 1992). Anorectal function and pelvic floor incoordination can be assessed by anorectal testing, anorectal manometry and a balloon expulsion test. For instance, in this way it has been possible to demonstrate pelvic floor incoordination in MS patients (Diamant et al., 1999; et al., Weber 1987; Jameson et al., 1994; Chia et al., 1996). To evaluate distal colon innervation, electrical rectal sensory testing is a useful tool. It can distinguish between constipation connected to impaired central innervation of the gut or idiopathic form (Kamm et al., 1990).

7. Pharmacological therapies

Several drugs are available for patients with chronic constipation, ranging from older over-the-counter laxatives to more recently developed prescription drugs (Lembo 2003; Longstreth 2006; Ramkumar et al., 2005; Rao et al., 2009; Tack et al., 2009; Tramonte et al., 1997). Laxatives stimulate defecation by decreasing stool consistency and/or by stimulating colon motility. There are different classes of laxative drugs with different mechanism of action: osmotic laxatives and stimulant laxatives, bulking agents, stool softeners (Ramkumar et al., 2005; Tramonte et al., 1997).

8. Fibers

Fibers intake such as eating high-fiber foods (fruits, vegetables) or taking fiber/bulk supplements (bran, psyllium, methylcellulose or polycarbophil) is recommended during the initial treatment of constipation (Lembo et al., 2003; Locke et al., 2000). Unfortunately a long treatment (about 2-3 months) is required to obtain symptom relief. Despite the widespread use of fiber supplementation, this approach is effective in only a subset of patients and clinical trial supporting the use of increased fiber intake is limited.

9. Osmotic laxatives

Osmotic laxatives (poorly absorbed/non-absorbed sugars, saline laxatives and polyethylene glycol [PEG]) cause intestinal water secretion and may be recommended when fiber therapy

is ineffective (Lembo et al., 2003). Many osmotic laxatives require few days to be effective and can result in electrolyte and volume overload in patients with renal or cardiac failure (Lembo et al., 2003). Osmotic laxatives can induce abdominal cramping, bloating and flatulence.

Osmotic agents are ions or molecules that are poorly absorbed by intestine and therefore they cause water retention in the intestinal lumen. Small intestine and colon are not able to keep an osmotic gradient between luminal contents and plasma, in contrast to stomach. Osmotic agents include: incompletely absorbed salts such as magnesium, sulphate and phosphate salts; sugar alcohols such as sorbitol or mannitol; poorly absorbed disaccharides such as lactulose and polyethylene glycol (PEG).

These agents keep water in intestinal lumen, increasing stool frequency, softening their consistency and decreasing straining. Non-absorbable sugars induce little improvement in stool frequency and consistency, but they cause colonic fermentation and consequently bloating and abdominal distention. Sodium sulphate reduces water absorption, stimulating peristalsis.

Bisodic phosphate is partially absorbed into the small bowel and it is well tolerated even if hyperphosphatemia can be observed as a consequence of overdose.

Magnesium hydroxide and magnesium salts improve stool frequency and consistency. Their systemic absorption is limited and the most common side effects are electrolyte abnormalities (i.e. hypokalemia and sodium overload) and diarrhea. In this light, magnesium should be used with great care in patients with hearth or/and renal failure and in the elderly (Golzarian et al., 1994; Schiller et al., 2001; Spinzi et al., 2007).

Lactulose is a complex sugar that is not digested and metabolized by bowel bacteria to form lactic, acetic and formic acids. In this way, it causes acidification of intestinal lumen, water secretion, production of H_2 and CO_2, and colon distension. Lactulose is very effective but induces flatulence and borborygmuses; moreover, its use should be avoided in patients with lactose intolerance.

In a systematic review of controlled trials, PEG was more effective than lactulose (Lee-Robichaud et al., 2010). PEG preparations are available with or without electrolyte supplements, and at different doses.

Macrogol 3350 is a mixture of non-absorbable polymers with high molecular weight. It is not metabolized by bowel bacteria and it works as a pure osmotic agent by keeping water into colon, causing rehydration and softer stool. The amount of water and electrolytes carried by macromolecular structure of macrogol is related to dose. The presence of electrolytes reduces risk of electrolyte imbalance, increasing safety in patients with kidney diseases (Migeon-Duballet et al., 2006). Moreover, macrogol causes less flatulence compared to lactulose, and it is useful for treating chronic constipation and drug-induced constipation (Di Palma et al., 2007; Zangaglia et al., 2007). Preparations containing electrolytes can also be used with high water volumes intake, such as for colon cleansing prior to colonoscopy or surgery (Di Palma et al., 2002; Szojda et al., 2007).

Glycerine is a well tolerated laxative, available just for rectal use. It works mainly by osmotic mechanism and stimulates evacuation lubricating stool.

Class	Active principle	Daily dose	Latency effect (hours)
Osmotic laxatives	Magnesium citrate	18g	0.5-3
	Magnesium hydroxide	2-4 g	6-8
	Magnesium sulfate	5-10g	6-8
	Sodium phosphate	10-20 ml /os 100ml/rectal	6-8 0.5-3
Sugars	Lactulose	5-30g	24-48
	Lactitol	10-15 g	24-48
	Sorbitol	5-15 g	24-48
	Mannitol	3-20 g	2-8
	PEG	15-40 g	24-48
	Glicerina	1-3 g	0.5
Diphenylmethane derivatives	Bysacodil	5-15 mg	10-12
	Sodium picosolfate	5-15 mg	6-10
Anthraquinone derivatives	Senna	24-48 mg	6-12
	Cascare	150-400 mg	6-12
	Rhubarb	50-100 mg	6-12
	Aloe	100-200 mg	6-12
	Frangola	200-600 mg	6-12
Surfactants	Docusate sodium	240 mg	0.5
Castor oil		15-60 ml	2-6

Table 1. Classification of laxative drugs

Stimulant laxatives (diphenylmethane and anthraquinone derivatives) produce rhythmic bowel contractions and should be recommended when osmotic laxatives fail (Borum et al., 2001). These agents increase intestinal motility and secretion after few hours from ingestion, but they may cause severe side effects (e.g. abdominal cramps, rebound constipation, damage to intestinal smooth muscles or enteric nervous system, colorectal cancer risk, hyponatremia, hypokalemia, dehydration. (Borum et al., 2001; Lembo et al., 2003; Muller-Lissner et al., 2005).

Several drugs and herbal preparations induce defecation by different mechanisms and are called 'stimulant' laxatives because they are able to stimulate bowel motility (Geboes et al., 1993). It is now clear that they have effect on mucosal transport as well as motility (Schiller et al., 1997).

These agents include: surface active agents, such as docusate and bile acids; diphenylmethane derivatives, such as phenolphthalein and bisacodyl; ricinoleic acid; anthraquinones, such as senna and cascara. Senna and bisacodyl cause rhythmic contractions of intestinal muscles, increasing bowel motility; moreover they increase water secretion into bowel. Bisacodyl is hydrolyzed in both small intestine and colon into a free-form that inhibits water absorption, but it also has an effect on enteric nervous system, inducing peristaltic response. Therefore, it should be avoided in patients with suspected intestinal obstruction. It is not clear whether these laxatives can induce damage to myenteric

plexus, whereas it is known that their chronic use is associated with colonic melanosis that is reversible with drug withdrawal (about 5-6 months).

Bisacodyl and picosulfate are both phenylmethane prodrugs, hydrolysed by colonic bacteria or brush border enzymes to their active metabolite bis-(p-hydroxyphenyl)- pyridyl-2-methane (BHPM) which stimulates peristalsis.

The cathartic activity of bisacodyl and sodium picosulphate may depend on their conversion to compounds with free diphenolic groups (Sund et al., 1981).

Phenolphthalein inhibits water absorption in small intestine and colon by effecting prostaglandins, kinins and the Na^+K^+-ATPase pump. Phenolphthalein is absorbed and can be undergone to an enterohepatic circulation which may prolong its effect. It has been withdrawn from sale in the United States because some studies in rodents suggested it may be carcinogenic (Garner et al., 2000; Josefson et al., 1997). Adverse reactions of derivatives of diphenylmethane are cramping and abdominal pain; high doses induce severe diarrhea, electrolyte depletion, damage to enterocytes, skin allergies and Stevens-Johnson syndrome (phenolphthalein).

Docusates are ionic detergents which were designed to allow water to interact more effectively with stool solids, thereby softening stools. Bile acids are natural detergents that have been used as components of proprietary laxative preparations. If exogenous bile acid is taken orally, normal ileal absorptive capacity may be enormous and sufficient bile acid may get to the colon to reduce water and electrolyte absorption or to stimulate water secretion.

Anthraquinones are a group of chemicals based on tricyclic anthracene nucleus. They are produced by different plants. Monoanthrones can form dianthrones and can be conjugated with sugars to yield glycosides. They are pro-drugs, not absorbed in small intestine and hydrolyzed by colon bacteria to active forms. The effects on water secretion with increased fecal water may appear about 6-8 hours after administration. These compounds are indicated to treat chronic constipation. Adverse drug reactions include allergies, loss of body fluid and electrolytes, reversible melanosis.

The laxative action of Castor oil is due to an irritant action on tenuous intestine by rinoleic acid released by hydrolysis of triglycerides by pancreatic lipase. It has several action mechanisms:

- Na^+-K^+-ATPase inhibition
- cAMP levels increasing
- mucose permeability increasing
- NO synthesis

Castor oil is used to preparation bowel for diagnostic or surgical procedures. Adverse reactions include abdominal-cramps and intestinal wall damage (e.g. erosion of the mucosa and epithelial desquamation).

10. Stool softeners

Laxatives which mostly soften or lubricate stools (e.g. sodium dioctyl sulfosuccinate and liquid paraffin) seem to be more effective than placebo to increase bowel movement frequency. Liquid paraffin, since it may interfere with absorption of fat-soluble vitamins, should be avoided in patients with oropharyngeal dysphagia (Gondouin et al., 1996).

11. Bulk lassatives

Undigestible fibres attract water, causing larger and softer fecal mass, increasing bowel movements by 1.4 per week (Ramkumar et al., 2005; Tramonte et al., 1997). Fibres are usually well tolerated, although some symptoms, such as bloating, may get worse.

12. Neuromuscular agents

Some patients with colonic inertia seem to have a reduction in cholinergic nerve activity. This could be due to a damage to the enteric nervous system or to agents with anti-cholinergic effects. In such instances it would be useful to increase cholinergic stimulation of colonic smooth muscle by supplying a cholinergic agonist agent. Bethanechol can be used for this purpose with good results in some patients. Neostigmine has recently been suggested as effective therapy for acute colonic pseudo-obstruction.

13. 5-HT4 receptor agonists

Serotonin (5-HT) is a regulator of gastrointestinal motility, secretion and sensitivity. Through 5-HT4 receptors, mainly expressed in enteric neurons, 5-HT triggers and coordinates intestinal peristalsis (Gershon et al., 2007). Cisapride, a 5-HT4 receptor agonist, is used to stimulate gastrointestinal motility in patients with gastro-esophageal reflux disease, functional dyspepsia and gastroparesis; in 2000, it was withdrawn from sale because of the occurrence of fatal arrhythmia's through QT interval prolongation in patients with predisposing conditions (Tonini et al., 1999).

Tegaserod, a 5-HT4 receptor agonist is shown to be effective for treatment of irritable bowel syndrome with constipation (Al-Judaibi et al., 2010). In 2007, Tegaserod was withdrawn from the commerce because of increased risk of cardiovascular adverse events such as myocardial infarction, unstable angina and stroke (De Maeyer et al., 2008).

Prucalopride, a 5-HT4 receptor agonist, is a highly selective compound. It enhances colonic transit in healthy control subjects and in patients with chronic constipation, in a dose-dependent way (Bouras et al., 1999; Bouras et al., 2001; Camilleri et al., 2008; De Maeyer et al., 2008). It has been approved in Europe for the treatment of chronic constipation in women who do not respond to laxatives (2 mg). Recommended dose in elderly patients is 1 mg for a larger bio-availability (Müller-Lissner et al., 2010).

The misoprostol affects intestinal transit in healthy subjects and in patients with chronic constipation by stimulating water secretion and intestinal muscle contraction, especially in the left colon. Initial dosage should be 200 mcg twice/day, increased to 4/day, being sure it does not appear abdominal cramps.

14. Colonic secretagogues

Lubiprostone, the last drug approved by FDA for treatment of adult patients with chronic idiopathic constipation (Bethesda et al., 2006), is a gastrointestinal system-targeted bicyclic functional fatty acid that acts as a selective chloride channel (ClC-2) activator in the apical membrane of gastrointestinal epithelium to increase intestinal water secretion (Orr et al., 2006; Winpenney et al., 2005). This enhanced secretion of chloride leads to an increased

intraluminal fluid amount, which facilitates transit in the intestine and thereby stool passage (Camilleri et al., 2006).

Lubiprostone, approved by FDA in 2006, is not yet approved in Europe (Drossman et al., 2009). Nausea, diarrhea and headache represent the most common adverse events, but patients also reported abdominal distension, abdominal pain and flatulence. Nausea can be reduced taking lubiprostone with food (Bethesda et al., 2006).

Linaclotide is a 14-amino acid peptide analog of guanylin and acts as an agonist at the luminal guanylin receptor on enterocytes, the guanylate cyclase-C receptor, which induces intestinal chloride and fluid secretion through cyclic GMP production (Bharucha et al., 2010). It is not yet approved for treatment of chronic constipation (Kurtz et al., 2006).

The mixed 5-HT4 receptor agonist/5-HT3 receptor antagonist renzapride relieves symptoms of constipation by softening stool consistency and increasing colonic transit. It has been tested only in patients with irritable bowel syndrome and constipation (Camilleri et al., 2004). Other 5-HT4 agonists, such as norcisapride and mosapride (Cremonini et al., 2005), neurotrophic factors (Coulie et al., 2000) and probiotic agents (Koebnick et al., 2003; Ouwehand et al., 2002) are also under investigations. Additional works are needed to determine their role in the treatment of chronic constipation.

Neurotrophins stimulate the development, growth and function of the nervous system, and increase colonic transit when administered subcutaneously in healthy subjects and patients with chronic constipation (Coulie et al., 2000).

Colchicine, usually used in the treatment of acute gout, induces diarrhea through an unknown dose-dependent mechanism. Colchicine increases stool frequency and reduces number of rescue laxatives needed. In a controlled trial, colchicine (1 mg/day) improved constipation in patients with slow transit (Taghavi et al., 2010).

15. Opiate antagonists

Opiate antagonists have also been suggested to treat constipation. These agents block opiate receptors in intestine avoiding mucosal absorption and inhibition of intestinal transit, caused by opiate. Thus mucosal absorption should be reduced and intestinal transit should be increase by the administration of drugs like naloxone and naltrexone. An early report suggested a role for this type of agent in idiopathic constipation, but a successive report denied it (Ragavan et al., 1983; Fotherby et al., 1987).

Opiate antagonists are useful in patients with opiate-induced constipation (Meissner et al., 2000; Yuan et al., 2000). The opiate antagonists methylnaltrexone and alvimopan are under investigation for the treatment of opiate-induced constipation and postoperative ileus, but unlike other opiate antagonists, they do not have any impact on central analgesia (Camilleri et al., 2005; Yuan et al., 2004). Their usefulness in treating non-opioid-induced constipation remains unclear.

16. Management of constipation in neurological disorders

Managing bowel function is a main concern in neurological patients, having an impact equal to mobility impairment on quality of life (Norton et al., 2010). It is important to get

information on current bowel status in order to provide an effective treatment (Gulick et al., 2011). The frequent coexistence of faecal incontinence represents a challenge in the management of constipation (Hinds et al., 1990). On the other hand, treatment of constipation is essential, because constipation itself may worsen bladder symptoms (Hinds et al., 1989). Treatment of bowel dysfunction in MS patients is often empirical and there are a few studies comparing the efficacy of different measures such as high fibre diet, adequate intake of fluids, bowel habits, physical exercise and the use of medication (Winge et al., 2003).

Increasing dietary fibre may be useful in MS patients to soften faeces, but it is not helpful in patients with severe constipation, as observed in spinal cord injury (Cameron et al., 1996). Furthermore the need for adequate fluid intake when taking bulking agents should be strongly encouraged. Sufficient or additional fluid intake and the use of docusate stool softener (up to 600 mg/day) are simple ways to help maintain soft bowel movements (DasGupta et al., 2003). On the other hand, a high fibre diet or the use of bulking agents may produce increased symptoms connected to the presence of increased fermentable substrate if peristalsis is impaired (Winge et al., 2003; Muller et al., 1988).

Stimulant or osmotic laxatives are useful when transit is slow. Senna and bisacodyl are effective and their dose can be modulated in order to avoid faecal incontinence, an effect reported more frequently with osmotic laxatives (Gattuso et al., 1994; Schiller et al., 1999).

Rectal stimulants such as glycerine or bisacodyl suppository, sodium citrate micro-enema or phosphate enema, have the advantage of predictability in terms of time of response as observed in patients with spinal cord injury or stroke (House et al., 1997; Munchiando et al., 1993).

Pelvic floor incoordination has been observed in MS patients (Mathers et al., 1990; Weber et al., 1987; Chia et al., 1996). Behavioural therapies – the so called biofeedback - have an important role in the management of constipation in this group of patients and they are effective in subjects with mild to moderate disability and a non progressive disease course. Over a third of patients considered themselves to have benefited in the medium term, but long term effects of biofeedback are unknown. There are no physiological test that can predict the response to this treatment (Wiesel et al., 2000; Munteis et al., 2008). Biofeedback improves pelvic floor function, conditioning the voluntary striated muscle sphincter response and patient's consciousness of a stimulus distending the rectum (Wiesel et al., 2000; Storrie et al., 1997).

Recently, in a randomized controlled study, some authors have suggested a beneficial effect of abdominal massage on constipation symptoms in MS patients (McClurg et al., 2011). Abdominal massage decreases severity of constipation and abdominal pain, and increases bowel movements. In health subjects with constipation, the massage has a delayed effect that may occur first after a number of weeks so that it is considered a long-term treatment. It does not lead to decrease in laxative intake, so abdominal massage could be a complement to medication rather than a substitute (Lämås et al., 2009).

For selected patients with severe constipation, when there is a lack of response to conservative therapies, colostomy or the Malone appendicostomy can be contemplated (Wiesel et al., 2001; Hennessey et al., 1999; Krogh et al., 2009).

In stroke patients Early physical activity should be recommended for stroke patients to prevent new-onset constipation (Su et al., 2009). The establishment of dedicated stroke units with early mobilisation, rehydration and diet regulating measures have resulted in a remarkable reduction of the problems related to constipation in stroke patients (Winge et al., 2003; Cardin et al., 2010; Kumar et al., 2010). A systematic assessment of bowel habits by nursing staff with a simple practice-based approach towards bowel management and patient/caregiver education has been shown to be helpful in patients with stroke (Harari et al., 2004).

A step by step approach, from simple to more complex treatment measures, is strongly recommended also in PD patients. Increasing daily fibre and fluid intake is the first step, since it is deficient in many patients with PD. Fibre supplements with psyllium or methylcellulose is useful and it significantly increases stool frequency and weight. The second step is to add a stool softener, such as docusate. Then patient can use an osmotic laxative, such as lactulose or sorbitol. Also the regular use of polyethylene glycol electrolyte balanced solutions is effective. It would be better to avoid irritant laxatives and enemas, even if they could be useful in selected cases (Pfeiffer et al., 2003).

Intrajejunal infusion of duodopa in patients with advanced-stage PD determine an improvement in constipation and other bowel symptoms in addition to other non-motor symptoms (Chaudhuri et al., 2009). Treatment of defecatory dysfunction in PD is more demanding. Laxatives do not improve the impaired anorectal muscular coordination and may increase the problem. Dopaminergic drugs may be useful, being observed an improvement in anorectal manometric during "on" periods, with deterioration when "off"' (Pfeiffer et al., 2003). Also apomorphine therapy can improve anorectal dysfunction in PD (Chaudhuri et al., 2009). Botulinum-toxin injections into the puborectalis muscle have been used successfully in the treatment of parkinsonian defecatory dysfunction. Faecal incontinence is a potential complication. Behavioural treatment approaches such as biofeedback training have not been specifically investigated in PD (Pfeiffer et al., 2003).

17. Conclusions

Bowel dysfunction is a frequent complication in neurological disorders and it can be due to neurological lesions or non-neurological causes. Owing to a complex physiopathology and to the involvement of autonomic system, a specific treatment is limited. A multimodal approach is needed to manage symptoms successfully and to provide individualized care for a particular patient. It is essential to determine realistic aims. Training bowel habits associated with physical activity, proper use of medication and biofeedback, just for selected patients, is an effective strategy to improve constipation in neurologic patients for some time, depending largely on disability level. Bowel management is still often empirical in neurological disorders and well-designed controlled trials are needed.

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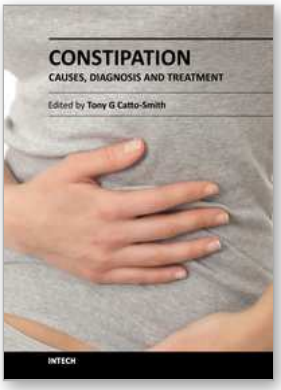

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Constipation is common in both adults and children. Estimates would suggest a median prevalence of around 12-16% in the general population. While regarded as a minor nuisance in some cases, its consequences can be severe, with a substantial impact on quality of life. Secondary faecal soiling has a profound psychological effect at all ages. This book provides contributions from authors with a range of backgrounds which clarify the pathogenesis, diagnosis, and therapy of constipation for the general population and also for certain high risk groups.

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