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## Management of opioid-induced bowel dysfunction in cancer patients

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**Abstract** The gastrointestinal (GI) effects of morphine and other opioids may result in opioid-induced bowel dysfunction (OBD) and the need for treatment. Although OBD is very common in morphine-treated patients, it is usually under-diagnosed. Opioids deliver their GI effect through central and peripheral mechanisms. Laxatives are the pharmaceuticals prescribed most in this area. Prokinetics as well as cholinergic agonists have been used satisfactorily. One-third of patients with OBD have to be treated rectally. The use of opioid antagonists has been favored, but the bioavailability of oral forms is poor. Opioid antagonists

with a quaternary structure have a high affinity for peripheral opioid receptors and therefore do not interfere with the analgesia, nor do they generate alkaloid withdrawal syndrome. Opioid rotation is another analgesic strategy directed toward decreasing the effects of previous opiates on the GI tract.

**Keywords** Opioid-induced bowel dysfunction · Morphine · Constipation · Laxatives

### Introduction

For the management of cancer pain, the World Health Organization (WHO) has implemented an analgesic ladder, which involves the use of potent opioid analgesics for the treatment of severe pain [61]. Orally administered morphine is the drug of choice for such purposes. However, the presence of side effects can play an important role in the success or failure of analgesic therapy in patients [8]. Consequently, there must be a balance between the analgesic effect of the morphine and the management of side effects [38]. Patients who are given morphine or other opioids chronically develop tolerance of these side effects; in the specific case of constipation, however, tolerance does not develop at the same rate. Thus, an initial prophylactic regimen is recommended in the administration of opiates. The gastrointestinal effects (GI) related to morphine and other opioids are due to a reduction in GI

motility caused by these drugs [53]. This produces gastric fullness, nausea, vomiting, hiccups, constipation, overflow diarrhea, and in some case mental confusion and delirium. Of these series of symptoms, constipation is the most frequent among patients treated with opioids [59] and is present in more than 50% of opiate-treated [55] patients. These series of GI symptoms constitute what is called opioid-induced bowel dysfunction (OBD) [36]. Despite aggressive laxative treatment, the constipation symptoms related to OBD are persistent in many patients.

A survey carried out by the American Pain Society found that in patients treated chronically, the incidence of constipation was five times higher [37]. This survey also showed that 58% of patients with chronic opioid use require more than two types of treatment for constipation.

## Physiopathology

The mechanisms by which opioids affect the GI tract have been clearly identified. Opioids cause constipation through a variety of mechanisms [50], including increased ileocecal and anal sphincter tone, as well as decreased peristalsis. Liquid and electrolyte absorption is increased, on the other hand, while defecation reflexes are decreased [50]. Three types of opioid receptors have been found in the central nervous system (CNS) as well as in the peripheral system:  $\mu$ ,  $\gamma$  and  $\kappa$ . In the GI tract, the  $\mu$  receptors are the ones most involved in the reduction of gastric emptying [11].

In terms of OBD physiopathology, opioids produce their effect through central and peripheral mechanisms [43]. With intraventricular cerebral administration of morphine in experimental animals, reduced intestinal transit has been observed [23, 27]. Morphine and other opioids inhibit the release of acetylcholine, thereby increasing intestinal tone and reducing peristalsis [24]. Opioids affect all levels of the GI tract [37]. Their action is due to a direct effect on the receptors at this level [25]. The stimulation of  $\mu$  receptors in the GI tract produces a decrease in intestinal motility and an antisecretion effect, the latter being considered the most important in OBD genesis. When stimulating gastrointestinal  $\mu$  receptors, morphine releases serotonin from neurons in the myenteric plexus [37]. The activation of 5-HT<sub>4</sub> receptors releases norepinephrine, which in turn activates  $\alpha_2$  receptors, consequently inhibiting enterocyte secretion [37].

## Assessment

Constipation and other symptoms resulting from OBD are related to comorbidity, cancer-associated factors and the drugs shown in Table 1 [22, 26]. Although constipation is one of the most frequent symptoms in morphine-treated patients, it is usually under-diagnosed. Because of this, questions must be asked regarding frequency of evacuation, previous laxative use, intestinal dysfunction-induc-

**Table 2** Radiological constipation score. The total score for all four quadrants is added. A score of 7 or more out of 12 indicates severe constipation

Score per quadrant	Amount of stool per quadrant
0	No stool
1	<50% of stool occupying the quadrant
2	>50% of stool occupying the quadrant
3	100% of stool occupying the quadrant

ing drugs, ingestion of liquids and concomitant illnesses [19]. Physical examination looks for palpable masses and anal sphincter tone in order to discount the presence of fecal impaction. Radiological assessment is very useful in determining the level of constipation by employing the constipation grading scale [45] (Table 2). This scale assesses the amount of fecal matter per quadrant for a maximum total of 3. A grade of 7 or more out of 12 points indicates severe constipation [5, 45].

## General measures

As much as possible should be attempted to correct the problem. If feasible, therapeutic schemes should be modified. Walking and activity should also be encouraged [47], and a comfortable, intimate environment provided where the patient can perform these functions.

## Pharmacological management

### Oral drugs

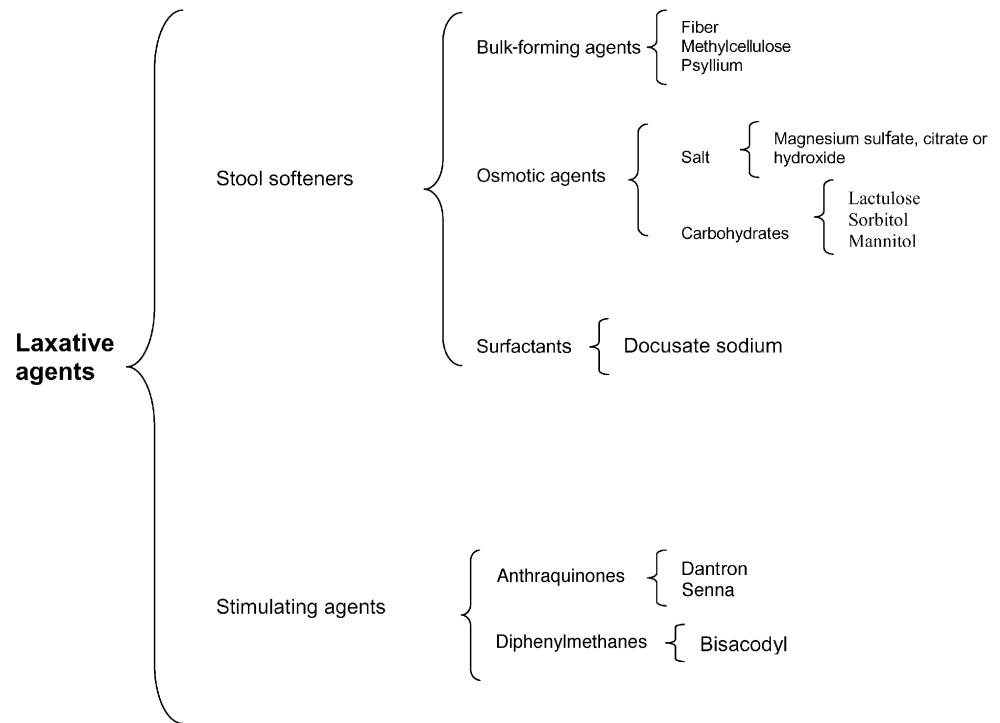
Laxatives are the drugs that have been prescribed most frequently in this area. In general, the way in which laxatives work boils down to these three mechanisms:

1. Increasing the amount of liquid in the intestinal lumen through osmosis or secretion [58].
2. Decreasing liquid and electrolyte absorption [46].
3. Increasing intestinal motility [46].

**Table 1** Constipation-related factors in cancer patients

Drugs	Cancer-related	Other diseases	Other factors
Vincristine	Tumor (mechanical obstruction)	Diabetes	Low-fiber diet
Corticosteroids	Spinal compression	Hemorrhoids	Lack of privacy
Nonsteroidal anti-inflammatory agents	Hypercalcemia	Anal fissures	Low liquid intake
Anticholinergic agents	Asthenia	Hypothyroidism	Age
Antidepressants	Depression	Cushing syndrome	
Diuretics	Proctitis post- radiotherapy	Fractures	
Opioids	Fatigue	Uremia	
Antihypertensive agents		Obesity	
Anticonvulsants		Depression	
Antihistaminic agents			

**Fig. 1** Classification of laxative agents



Laxatives are classified into two main groups: intestinal motility-stimulating agents and stool-softening agents. The latter is divided into osmotic, surfactant and bulk-forming agents, as shown in Fig. 1 [46].

The most common bulk-forming agents are fiber and methylcellulose. These agents increase the formation of fecal matter with substances that are not absorbed in the GI tract or degraded by enteric flora. These augment the volume of fecal matter, thereby producing a stretching reflex which favors intestinal transit. On the other hand, these agents generate a substratum for bacteria, encouraging fermentation and gas formation, which in turn add to intestinal motility [7]. When these agents are administered, the patient must drink 200–300 ml of water [50], as well as a further liter of water daily. As a result, these agents are not useful for patients with advanced cancer with an impaired functional status, due to their inability to manage high volumes of liquids. Improvement with chronic use of these drugs is modest, and severe cases of constipation do not react substantially [33, 51]. Psyllium, another agent in this group, is a gelatinous mucin compound which acquires a viscous consistency in water [26]. It joins bile salts in inhibiting fat absorption. Among the side effects caused by these agents are flatulence, allergies, and worsening constipation if not enough liquid is ingested [50, 51, 53].

The osmotic agents can be divided into saline agents and carbohydrates. Saline agents produce effects throughout the entire GI tract, while carbohydrates are degraded in the colon by the bacterial flora. These drugs are not ab-

sorbed in the GI tract and their action, as the name suggests, takes place through osmosis, increasing the amount of water in the intestinal lumen [50]. Lactulose and sorbitol are the osmotic carbohydrates most commonly used. Lactulose has the inconvenience of being too sweet. Not all patients tolerate lactulose, specially when we consider that up to 60 ml is needed sometimes to obtain appropriate GI function [48]. Magnesium salts are the most commonly used salt agents (milk of magnesia). However, chronic use of these agents is not recommended since they interfere with nutrient and medication absorption. Stimulating agents are anthraquinones and diphenylmethanes. Dantron, senna and *casacara sagrada* are members of the anthraquinone group, while bisacodyl and phenolphthalein are important members of the diphenylmethane group. These agents encourage peristalsis and partially inhibit ATPase  $\text{Na}^+$ ,  $\text{K}^+$  [6, 50] activity. The GI tract absorbs approximately 15% of these drugs.

Abdominal cramps are frequent with the use of these pharmaceuticals [48]. Senna is degraded in the colon by bacteria, resulting in the active aglycones which give this drug its laxative properties; hence, the use of anthraquinones in the colon is limited. Anthraquinones have been reported to damage myenteric nerves; the evidence for such damage, however, has not been conclusive in every case [54]. Colonic melanosis resulting from the presence of an accumulation of apoptotic epithelial cells that have been phagocytosed by macrophages [20] has been reported when these drugs are used. No important differences have been found when comparing the effec-

tiveness between osmotic and stimulant agents such as lactulose and senna [1, 29]. Notwithstanding, simultaneous use of both agents produces a superior effect [48].

Agents such as paraffin and mineral oil are used as lubricants for fecal matter and also soften its consistency. Prokinetics such as cisapride, domperidone and metoclopramide, and cholinergic agonists such as bethanecol, have been used satisfactorily [28, 32]. These medicines can be used simultaneously with laxatives to combat OBD symptoms such as nausea and vomiting. When administered as a continuous subcutaneous infusion, metoclopramide can effectively resolve OBD [4]. Both metoclopramide and domperidone produce their effect by inhibiting dopamine centrally and peripherally [3, 16]. As a principal effect produced by these drugs, peristalsis in the digestive tube is inhibited.

Chronic use of metoclopramide can be associated with extrapyramidal syndromes. It is important to underscore that in some countries, domperidone has been removed from the market due its effect in prolonging the Q–T interval [12]. Cisapride itself acts by stimulating 5-HT<sub>4</sub> receptors, and thus has a prokinetic effect. Cisapride acts along the entire GI tract and has proven to be the most efficient medicine for OBD treatment [41]. Since cisapride can cause helicoidal tachycardia, it has also been taken off the market in several countries. Tegaserod is another agent that acts as a partial 5-HT<sub>4</sub> agonist and has demonstrated effectiveness in the treatment of constipation [34]. However, there are no reports of its use in patients with OBD.

#### Pharmaceuticals for rectal administration

Close to one-third of patients with OBD have to be treated rectally [52]. Suppositories, enemas, and manual and mechanical handling are some of the available methods. Among the manual techniques is digital disimpaction. Suppositories, on top of the drug's intrinsic mechanisms, produce anal-rectal stimulation, thus stimulating defecation. Glycerol suppositories lubricate the intestinal mucosa. Bisacodyl by itself or in combination with glycerol is useful, given its previously mentioned contact mechanism. Because of this, suppositories are recommended to help initiate defecation. Rectal enemas should be administered as rescue methods when the above approaches fail.

A comparison between 130 ml phosphate enemas and mini-enemas demonstrated similar efficiency of both [39]. It is therefore recommended giving the latter to patients whose constipation persists despite previous use of laxatives, or to those who have not had a bowel movement and have soft feces [50]. High-volume saline enemas are recommended for patients with fecal impaction [49]. In these patients, the enema should be administered at the highest descending point and not in the

rectum or anus, since otherwise the enema content would exit immediately [14]. The contents must be retained for at least 10 min for fecal matter to be easily expelled [13].

#### Other alternatives

##### Opioid antagonists

The use of opioid antagonists is encouraged because of the poor bioavailability of these agents. Thus, the amount of this drug that crosses the blood-brain barrier (BBB) is minimal and no antagonism is observed in the CNS receptors [49]. Several studies have shown that naloxone is effective in OBD [2, 9, 29, 30, 46]. The dose range used to reduce the incidence of OBD varies: an 8–10 mg dose [2], or 10–20% of the daily morphine dose [19, 30]. In order to prevent the opioid withdrawal syndrome (OWS) and slowly increase the amount of drug to obtain a satisfactory response, an initial maximum dose of 5 mg is recommended [47]. Nonetheless, most studies have shown the presence of OWS as the dose of naloxone is increased [9, 15, 30, 47]. Other strategies have been used to reduce the occurrence of OWS. One of these involves the use of antagonist agents with quaternary structures. Such agents act peripherally, since they do not cross the BBB. Methylnaltrexone, a quaternary derivative of naltrexone, is one of these agents. Methylnaltrexone has a high affinity for peripheral opioid receptors, and therefore does not interfere with analgesia, neither does it produce OWS, even with parenteral administration [35, 62, 63]. A lower incidence of OBD-related nausea, vomiting and constipation has been observed with the use of this drug, as well as of other peripheral, opioid-induced effects.

Alvimopan (ADL 8-2698) is another opioid antagonist with peripheral effects [42]. This agent has more affinity for  $\mu$  receptors than naloxone [42]. In the beginning it was observed that this agent could reverse loperamide-induced constipation in healthy patients [64]. Another study was conducted to assess the effect of alvimopan on morphine-induced analgesia [21] in patients undergoing dental surgery. This agent did not have an effect on morphine-induced analgesia, and intestinal transit increased with respect to those patients who were given only morphine [21].

##### Miscellaneous drugs

Colchicine is a drug traditionally used to treat acute gout. This pharmaceutical causes profuse diarrhea if conventional doses used for acute gout are administered. This is why it has been used to treat chronic constipation [56, 57]. Erythromycin has been successfully used in patients with diabetic gastropathy [18]. It encourages intestinal transit by stimulating motilin receptors [17]. Misoprostol is a synthetic prostaglandin used to prevent peptic ulcers

associated with the use of nonsteroidal antiinflammatory drugs. It produces diarrhea in 25–30% of patients who use it for this purpose [44]. As a result, it has been used in hard-to-treat chronic constipation.

It should be pointed out, however, that there is no reliable evidence that this group of drugs is effective in the treatment of OBD.

### Opioid rotation

The principle of opioid rotation consists of changing the alkaloid in order to maintain or improve analgesic quality and to reduce the adverse effects caused by the opioid with which treatment began [8]. As an opioid's intrinsic activity increases, the requirement decreases [31]. If fewer receptors are used, one would expect a lower incidence of adverse effects. Tramadol has less impact on the GI tract than morphine. However, the potency of tramadol is that of a weak analgesic, so that in some cases it would not meet the analgesic requirement [60]. Rotating to methadone reduces laxative consumption [10]. This is probably because methadone has less affinity for peripheral receptors than morphine. Fewer occurrences of constipation and less laxative consumption have been observed with the use

of transdermal fentanyl in comparison with orally administered morphine [40].

### Discussion

OBD is a frequent complication in patients with opioid-treated chronic pain. In many cases this problem is not given the importance it deserves, so the related complications may be increased. The functional state of cancer patients deteriorates as constipation increases [13, 28]. Likewise, when inadequately treated, OBD produces pain, which in turn generates increased opioid consumption, thus perpetuating OBD. As more symptoms appear, the patient may experience a state of confusion. That is why pushing ahead with a laxative or prokinetic prophylaxis program is always recommended with every patient under alkaloid therapy. If these methods do not give good results, one of the others mentioned above can be employed. Nonetheless, we must not forget that a patient's reduced gastric emptying may have a cause other than the use of opioids.

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