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Management of Opioid Induced Constipation

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Abstract

Up to 40% of patients taking opioids develop constipation. Opioid induced constipation (OIC) may limit the adequate dosing of opioids for pain relief and reduce quality of life. Hence, healthcare providers must inquire about bowel function in patients receiving opioids. The management of OIC includes carefully reevaluating the necessity, type, and dose of opioids at each visit. Lifestyle modification and alteration of aggravating factors, the use of simple laxatives, and when essential, the addition of newer laxatives or opioid antagonists (naloxone, naloxegol or methylnaltrexone) can be used to treat OIC. This review discusses the recent literature regarding the management of OIC and provides a rational approach to assessing and managing constipation in individuals receiving opioids.

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Introduction

Up to one third of the population in the western world report chronic pain (Johannes *et al*, 2010). For these individuals, effective analgesia alleviates suffering, promotes functionality and improves quality of life. In principle, the simplest and safest analgesic medication which provides adequate relief should be used. However, simple analgesics (e.g. acetaminophen [paracetamol] or non-steroidal anti-inflammatory drugs) provide insufficient relief for many individuals with chronic pain (Moore *et al*, 2013; Machado *et al*, 2015). For others, simple analgesics are avoided in view of their adverse gastrointestinal or cardiovascular risk profiles (Lanas *et al*, 2010). Consequently, opioid analgesia is prescribed. Although potentially effective in relieving pain (Mercadante, 1999) and improving quality of life (Klepstad *et al*, 2000), opioids are associated with different side effects compared to simple analgesics.

Adverse effects associated with opioids are frequent and affect numerous organ systems. Within the gastrointestinal system constipation, nausea, vomiting, reflux, and bloating are reported (Bell *et al*, 2009). Among the opioid side effects, constipation is the most frequent. It may be more severe (i.e. less frequent bowel motions, harder stools, more straining and a greater sense of incomplete evacuation) than constipation unrelated to opioid use. Additionally, unlike many other opioid side effects (e.g. nausea), the severity of opioid induced constipation (OIC) does diminish over time with ongoing opioid administration (i.e. tolerance does not develop) (Bell *et al*, 2009). The severity of OIC, and other adverse effects, can limit effective dosing of opioid analgesics (Bell *et al*, 2009). Adverse effects can therefore negatively impact activities of daily living and quality of life. In general, there are two options for managing these side effects, i.e., reducing or discontinuing opioid administration or using other measures to treat side effects.

As the prevalence of chronic pain and use of opioid medications increases in society (Zin *et al*, 2014), health care providers need to be versed in the appropriate use of opioids as well as preventing and managing OIC.

Physiology of Opioid Induced Constipation

A comprehensive description of the physiological effects of opioid agonists and antagonists is reviewed elsewhere.{Wood, 2004 #167} Briefly, opioid receptors are the natural ligand for endogenously produced neurotransmitters. There are three types of receptors (μ , δ or κ receptors), distributed throughout the central, peripheral and enteric

nervous systems. Analgesia is achieved through stimulation of central μ opioid receptors. However, stimulation of μ receptors in the enteric nervous system results in adverse gastrointestinal effects, specifically because of i) increased pyloric, anal and biliary sphincter tone, ii) reduced enteric, biliary, and pancreatic secretions, iii) increased water absorption from the bowel and, iv) reduced gastric emptying and reduced propulsion of chyme through the intestine (De Schepper *et al*, 2004). Individually, and in combination, these physiological changes promote constipation. However, the acute effects of various opioids on gastrointestinal function and symptoms vary. For example, although codeine, oxycodone and tapentadol all cause constipation, only codeine delays colonic transit (Gonenne *et al*, 2005; Jeong *et al*, 2012). When compared to oxycodone, tapentadol appears to cause less constipation, nausea and vomiting (Stegmann *et al*, 2008).

Assessment

Clinical

Some patients with constipation may not volunteer the symptom. Therefore, during each healthcare interaction with patients taking opioids, they should be questioned regarding bowel motion frequency, consistency, straining, completeness of evacuation and satisfaction with their bowel habit. The precise questions, which are detailed elsewhere {Longstreth, 2006 #168}, have been validated in ambulatory people but not in opioid-induced constipation. Responses to these questions should be documented to facilitate subsequent comparisons and treatment should be initiated if required.

A systematic review of fifteen randomised, placebo-controlled trials of opioids observed that constipation (41%), nausea (32%) and somnolence (29%) were the most common side effects (Kalso *et al*, 2004). Although specific populations (e.g. older patients and those with cancer related pain) may have a greater risk of developing OIC (Rosti *et al*, 2010; Ishihara *et al*, 2012), constipation should not be attributed to opioid administration by default. OIC is defined as “a change when initiating opioid therapy from baseline bowel habits that is characterised by any of the following: reduced bowel movement frequency, development or worsening of straining to pass bowel movements, a sense of incomplete rectal evacuation, or harder stool consistency” (Camilleri *et al*, 2014). The temporal association between initiation or escalation of the dose of opioids and a change in bowel habit is required to establish the diagnosis. Without this clear association other structural, functional, pharmacological and biochemical causes (Table 1) should be excluded as

necessary (and as appropriate for the underlying condition and overall prognosis) as constipation is a common symptom in the general population (Bharucha *et al*, 2013).

A meticulous examination of both the anal canal and rectum is mandatory during initial assessment to identify conditions causing, or contributing to, constipation. Within the anal canal, pathology affecting the mucosa (anal fissures) or poorly coordinated muscular function (dyssynergia) should be sought. The rectum should be evaluated for faeces (possibly suggesting faecal impaction) or neoplastic masses (Talley, 2008).

Investigations

Investigations are recommended when constipation does not respond to simple laxatives. When investigation of constipation is required, (i.e. not clearly associated with opioid use) the initial assessment should include a complete blood count and sodium, calcium, potassium and thyroid stimulating hormone levels (Bharucha *et al*, 2013). In individuals in whom adrenal failure is suspected, cortisol levels should be assessed. In general, endoscopic evaluation (colonoscopy or sigmoidoscopy) is probably unnecessary in patients with an advanced illness and OIC. However, these investigations should be considered when there is a strong index of suspicion for colorectal cancer, such as unexplained weight loss or significant rectal bleeding that cannot be explained by the underlying condition. A plain abdominal X-ray can be useful to identify faecal impaction and/or bowel obstruction. Cross sectional imaging (e.g., computed tomography or MRI) should be considered only if there is concern for sigmoid volvulus, malignant colonic obstruction or an intra-abdominal mass. In patients with constipation refractory to laxatives, anorectal manometry and a rectal balloon expulsion test are generally recommended to identify defecatory disorders such as functional outlet obstruction, which are treated with biofeedback therapy (Bharucha *et al*, 2013). Barium defecography can also be used for this purpose.

Prevention of OIC

Prophylactic laxatives are recommended at the time of, or before, opioid prescription to prevent OIC. While sensible, there is little research to support this practice. A single trial of 619 hospitalised patients from Japan reported that the use of laxatives before opioids were initiated was associated with a lower incidence of constipation, defined as more than 72 hours without a bowel motion (34% vs. 55%, Odds Ratio 0.43, 95% CI 0.30-0.62)

(Ishihara *et al*, 2012). Although the majority of patients received an osmotic laxative (magnesium oxide), with or without a stimulant laxative, the use of laxatives was not standardised. In addition, the trial was short, only hospitalised patients were included and neither other symptoms of constipation (e.g., excessive straining) nor the impact of this intervention on quality of life were assessed. Nonetheless, the high incidence of OIC and its impact on quality of life justifies this intervention.

Management of OIC

We recommend a stepwise approach to managing OIC commencing with modification of lifestyle factors and precipitants. Simple laxatives can be added simultaneously or sequentially as needed. Symptoms should be re-evaluated at intervals sufficient for the effects of laxatives to become apparent. The psychological aspects of the underlying disease should also be evaluated and managed. A careful evaluation of the patient's understanding regarding their constipation and underlying disease, with teaching, explanation and supportive reassurance, where required, can be of benefit in treating physical symptoms and influencing opioid use (Adams *et al*, 2006; Richardson *et al*, 2006).

Exclusion and Treatment of Underlying Precipitants and Disorders

The initial management of constipation should focus on treating underlying causes and reducing aggravating factors. For example, endocrine or metabolic disturbances should be treated and medications that exacerbate constipation should be discontinued or replaced with non-constipating alternatives where possible (Bharucha *et al*, 2013). Lifestyle choices which promote healthy bowel habits should be encouraged although limited evidence exists to support practice. Increasing dietary fibre content should be considered but can cause or increase abdominal bloating. Hydration and physical activity should be encouraged. One study suggested that immobility may have a greater constipating effect than opioid medications (Fallon, 1999). For patients with reduced mobility, the use of a bedpan is associated with constipation; hence this should be avoided when possible (Su *et al*, 2009).

Optimisation of Opioid Administration

In our opinion, the long term use of opioids in patients with non-cancer non-palliative pain (e.g. chronic abdominal pain, fibromyalgia) should be strongly discouraged. In these

patients, other multidisciplinary approaches to manage pain are often more effective and definitely safer (Chaparro *et al*, 2013). Where opioids are required, administration can frequently be optimised in patients experiencing adverse effects. To achieve this, at every visit, the requirement for opioids, the dose, and type of preparation should be reassessed.

Patients who do not experience pain relief after an adequate trial of opioids are unlikely to achieve satisfaction with this class of medication (Stannard, 2013). In this situation, the risk of adverse effects outweighs the benefits. Opioids should be tapered and alternative approaches to pain management initiated (American Society of Anesthesiologists, 2010; Franklin, 2014).

Limited evidence suggests that the incidence of OIC is associated with higher (Knezevic *et al*, 2014) and more frequent (Bell *et al*, 2009) opioid dosing. When opioids have relieved pain but caused adverse effects, the addition of analgesic adjuncts may facilitate opioid dose reduction. Non-opioid analgesics (acetaminophen or NSAIDs) are simple pharmacological adjuncts (Caraceni *et al*, 2012). Anti-depressant or anti-epileptic medications may benefit patients with neuropathic pain (Bennett, 2011). Non-pharmacological adjuncts (e.g. meditation, cognitive behavioral therapy [CBT], neurostimulators) may also be of benefit (Park and Hughes, 2012). CBT approaches such as The Pain Plan are increasingly being commissioned from pain teams in the UK (Cole *et al*, 2012).

Where opioids have relieved pain and dose reduction is not possible, consideration should be given to opioid switching as adverse effects vary amongst opioids and by route of administration. Morphine is associated with a higher incidence of GI side effects than many other opioids (Cook *et al*, 2008; Ishihara *et al*, 2012). Tapentadol, which is a μ opioid agonist that also inhibits norepinephrine reuptake, was as effective as oxycodone for managing chronic moderate to severe skeletal pain (Lange *et al*, 2010), but has fewer side effects (Stegmann *et al*, 2008). The incidence of constipation is lower for transdermal fentanyl than an equianalgesic dose of oral morphine (Tassinari *et al*, 2008).

Laxatives for the Treatment of OIC

Simple laxatives are inexpensive and often effective for preventing and managing OIC. In our practice, treatment is initiated with regularly administered osmotic agents (e.g., polyethylene glycol or milk of magnesia). Additionally, a stimulant laxative (e.g. bisacodyl, senna, glycerine suppository or an enema) is administered on an as-needed basis if patients

do not have a bowel movement for 2 days. However, there is a limited amount of information regarding the efficacy of simple laxatives in OIC.

One small study suggested that lactulose, senna, and codanthrusate were of comparable efficacy in treating opioid (loperamide) induced constipation in healthy volunteers (Sykes, 1996). In one survey, the prevalence of constipation was greater (40%) in 76 patients receiving opioids compared to a control group of 10,018 individuals (8%) from a different study (Pappagallo, 2001). Among these constipated individuals, a greater proportion of opioid users were taking laxatives (80% versus 55%). However, a smaller proportion of opioid users (46% versus 84%) reported a satisfactory response to laxatives more than 50% of the time (Pappagallo, 2001). In another study of 322 patients concurrently taking both laxatives and opioids, “constipation” was reported by 81%. Among the cohort, 45% reported fewer than 3 bowel motions per week, 58% reported straining, 50% reported too small/hard bowel movements and 45% reported incomplete evacuation. Use of more than one laxative was reported by 45% of the group (Bell *et al*, 2009). Additional studies comparing the response to simple laxatives in OIC and non-OIC constipation would be useful.

Where simple laxatives are insufficient to relieve OIC, consideration can be given to using lubiprostone or prucalopride. Lubiprostone stimulates intestinal fluid and electrolyte secretion by activating type 2 chloride channels. It is approved by the USA Food and Drug Administration (FDA) for treating refractory constipation and OIC in non-cancer pain. In the United Kingdom, it is only licensed for the treatment of refractory constipation. In one randomised double blind placebo controlled trial of patients taking stable doses of opioids for non-cancer pain, 24 micrograms of lubiprostone administered twice daily increased the number of bowel motions per week at 8 weeks (by 2.2 for lubiprostone versus 1.6 for placebo, $P = 0.004$). Lubiprostone was also more effective than placebo for reducing straining, abdominal discomfort, and stool consistency but not bloating (Cryer *et al*, 2014). However, there was no difference in the use of “rescue” medications for constipation between lubiprostone and placebo. Furthermore, at 12 weeks, differences between lubiprostone and placebo were not significant suggesting the possibility of tolerance. Prucalopride, a selective 5-HT₄ agonist, is also effective for treating OIC. Among patients with chronic non–cancer pain suffering from OIC, 69% of patients receiving 4mg of prucalopride passed ≥ 3 spontaneous bowel motions per week (compared to 43% of patients receiving placebo) after 4 weeks treatment (Sloots *et al*, 2010). However, it is not approved by the FDA and in the United Kingdom is only approved for the treatment of refractory constipation. Unfortunately, lubiprostone and prucalopride have only been compared to

placebo. Consequently, the incremental benefit of these drugs over simple laxatives is unknown. Additionally, their efficacy in OIC related to cancer pain is unknown.

Treating OIC with Opioid Antagonists

Naloxone is a central and peripheral acting opioid receptor antagonist that is efficacious for treating OIC (Meissner *et al*, 2000). This medication can be administered separately from opioid medications or as a premade fixed dose combination tablet. With fixed dose combinations of an opioid agonist and naloxone, it is not possible to individually titrate the analgesic effects of opioids and laxative effects of naloxone. The effects of naloxone are predominantly limited to the intestine due to a high first pass metabolism. Naloxone therefore inhibits stimulation of μ opioid receptors within the gastrointestinal tract without substantially altering the analgesic efficacy of opioids. However, in patients with impaired liver function (e.g. cirrhosis or metastatic burden), the first pass metabolism of naloxone is reduced and its bioavailability is increased. As naloxone can cross the blood brain barrier, opioid withdrawal and loss of analgesic effect may occur in this situation (Burns *et al*, 2014).

To reduce the likelihood of withdrawal and loss of analgesic effect, naloxone has been conjugated with a polyethylene glycol moiety (Naloxegol), which reduces its ability to cross the blood brain barrier. Oral naloxegol (25 mg once daily) was effective for treating OIC in adults taking opioids for chronic non-cancer pain. In two large studies (total 1352 participants), the frequency of spontaneous bowel movements increased in 40% and 44% of patients. This was 10 - 15% greater than the response rate to placebo (Chey *et al*, 2014). Straining and stool consistency were also improved. Among the cohort of patients refractory to laxatives, the response rate was greater (47% and 49%). Given the stringent definition of response in these studies (three or more spontaneous bowel movements per week, without the use of bisacodyl or an enema in the previous 24 hours, and an increase of one or more spontaneous bowel movements over baseline for at least 9 of 12 treatment weeks and at least 3 of the final 4 treatment weeks), the benefit of this medication in clinical practice may be greater. However, adverse events were frequent in these trials, occurring in over two thirds of patients and resulting in naloxegol discontinuation in 10%. The most common were abdominal pain (19%), diarrhea (9%), nausea (9%) and flatulence (6%). Symptoms possibly consistent with opioid withdrawal (eg, hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, irritability, and yawning) were reported in patients treated with naloxegol and may be more frequent in patients receiving methadone and among patients with disruptions to the

blood-brain barrier. Naloxegol is approved by regulatory agencies in the European Union (EU) and United States (US) for treating OIC in adult patients with chronic non-cancer pain.

The peripherally acting μ opioid receptor antagonist (PAMORA) methylnaltrexone blocks only peripherally located μ opioid receptors. Therefore it restores gastrointestinal function with minimal effects on the centrally mediated analgesic properties of opioids. Methylnaltrexone is currently licensed in the US and EU for treating OIC in adults. In the EU, the license specifies that patients must have failed to respond to other laxatives. Approval was based on efficacy demonstrated in two double-blind randomised placebo-controlled trials (Thomas *et al*, 2008; Michna *et al*, 2011). During these trials, patients treated with methylnaltrexone reported less distress related to constipation and an improved quality of life. In the first trial, among patients with an advanced illness (60% had cancer), a single dose of methylnaltrexone (0.15mg/kg) was superior to placebo in inducing a bowel motion within 4 hours of administration (48% versus 15% of patients respectively) (Thomas *et al*, 2008). However, the proportion of patients with rescue-free laxation within 24 hours of dose administration was not significantly different between methylnaltrexone and placebo after the first four doses administered on alternate days. During the subsequent 12 week open label extension study, the response rate was approximately 50%. Patients who had a more pronounced initial response, as manifest by a response to ≥ 2 of the initial doses, were more likely to respond to subsequent doses over 12 weeks. Similar findings were reported in the second double-blind trial in patients with non-cancer chronic pain (Michna *et al*, 2011). In these trials there was only a minimal reduction in the use of simple laxatives.

In these trials, mild to moderate abdominal pain (the most frequent side effect) was reported by up to 20% of patients (Thomas *et al*, 2008; Michna *et al*, 2011). Nausea, vomiting and flatulence were each reported in over 10% of patients. A reduction in opioid analgesic efficacy has been observed with supra-therapeutic doses (Jagla *et al*, 2014) but has not been identified in clinical trials of OIC. Although a review of the FDA Adverse Event Reporting System database identified 7 patients (from April 2008 - October 2009) who had bowel perforation while receiving methylnaltrexone (Mackey *et al*, 2010), some of these patients had an underlying organic GI disorder or surgery (e.g., metastatic colon cancer, volvulus) and during the period approximately 14,000 patients were billed for the medication. Taken together, these findings do not demonstrate that methylnaltrexone leads to bowel perforation.

In contrast to naloxone, methylnaltrexone is available only as a subcutaneous injection. Although an oral preparation of methylnaltrexone was efficacious in pilot studies, it is not available for clinical use (Rauck *et al*, 2012). Currently, dosing recommendations vary

slightly between the US and EU. In the US, the recommended dose, given subcutaneously every second day as needed, is 0.15 mg/kg for patients weighing less than 38 kg and more than 114 kg, 8 mg for patients weighing 38 to 62 kg, and 12 mg for patients weighing 62 to 114 kg. Dosing frequency can be increased to every 24 hours if required. The European Medicines (Evaluation) Agency Assessment Report recommends that methylnaltrexone can be given as two consecutive doses 24 hours apart, but thereafter, the dosing frequency should return to every 48 hours. Dosing at the 24 hour interval should be used only in exceptional circumstances. Although a dose response curve to methylnaltrexone has not been reported, there is a suggestion that patients with non-cancer pain and/or who require a morphine equivalent dose greater than 150mg daily at baseline may respond more favorably to 0.3mg/kg of methylnaltrexone than the 0.15mg/kg dose (Nalamachu *et al*, 2014). Additionally, some studies suggest that different doses of opioid antagonists may be required for treating acute and chronic OIC (Camilleri *et al*, 2014). In one study, 0.3 mg/kg methylnaltrexone (a dose greater than that effective for treating OIC in clinical trials) was ineffective in attenuating the gastrointestinal effects of acute codeine administration in healthy volunteers (Wong *et al*, 2010). Further research is needed to clarify these issues.

To maximise its therapeutic benefit, methylnaltrexone should only be used only after trials of standard laxative therapies have failed. It is less effective in patients who have co-existent modifiable risk factors (e.g. medications, hypercalcemia) for constipation (Clark *et al*, 2012). Furthermore, in patients who respond to fewer than two of the initial four doses of methylnaltrexone, there may be little benefit in continuing the medication (Thomas *et al*, 2008).

Management of Faecal Impaction

Faecal impaction is a common cause of constipation, especially in patients receiving opioids. A rectal examination will usually reveal hard impacted stool in the rectal vault. A plain X-Ray of the abdomen also provides a qualitative estimate of the amount of stool in the colon. These patients are unlikely to respond to oral therapy. Per rectal measures (e.g. starting with sodium phosphate enemas and progressing to tap water enemas or manual disimpaction) are advisable. After resolution of the impaction, therapy should commence with simple laxatives with escalation as clinically warranted.

Conclusion

Constipation is a common symptom among patients and may limit the ability to provide an adequate dose of opioids. Patients receiving opioids may not volunteer the symptom – hence they should be asked about their bowel habits. Consideration should be given to identifying, as appropriate, other causes of constipation in patients taking opioids. Prophylactic laxatives should be administered in an attempt to prevent OIC. If OIC is diagnosed, lifestyle factors should be optimised and simple laxatives and/or per rectal measures (suppositories, enemas) should be used. When feasible, consideration should be given to discontinuing or altering the dose of opioids or switching to an alternative preparation. Adjunctive analgesia should be utilised. Re-evaluation should be performed after each intervention and therapy escalated as warranted by adding newer laxatives, naloxone or methylnaltrexone to a consistent regimen of simple laxatives. Where these medications are required, patients must be monitored for laxative associated side effects and loss of opioid analgesic efficacy.

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Cause	Examples	
Chronic constipation	Slow transit constipation, defecatory disorders, constipation predominant irritable bowel syndrome	
Constitutional factors	Immobility, dehydration	
Medications	Analgesics	Opioids, Non-steroidal anti-inflammatory drugs (NSAIDs)
	Anticholinergics	Dicyclomine, Benzotropine, Diphenhydramine, Chlorpromazine, Amitriptyline
	Antihypertensives	Amlodipine, Atenolol, Verapamil, Nifedipine
	Antiemetics	Ondansetron
	Minerals	Aluminum, Calcium, Iron, Lithium
Endocrine disorders	Diabetes, hypothyroidism	
Metabolic disturbances	Hypercalcemia, hypokalemia, hyponatraemia	
Neurological disorders	Parkinson's disease, multiple sclerosis, autonomic neuropathies	
Colonic strictures	Colorectal cancer, post-radiotherapy, extrinsic compression from intra-abdominal tumor	

Table 1. Common causes of constipation