A Review of the Clinical Manifestations, Pathophysiology and Management of Opioid Bowel Dysfunction and Narcotic Bowel Syndrome

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ABSTRACT

Opioids are widely used for the treatment of malignant and non-malignant pains. These medications are accompanied by adverse effects, in particular gastrointestinal symptoms known as opioid bowel dysfunction (OBD). The most common symptom of OBD is refractory constipation that is usually stable regardless of the use of laxatives. Narcotic bowel syndrome (NBS) is a subset of OBD described as ambiguous chronic pain aggravated by continual or increased opioid use for pain relief. Pathophysiology of these disorders are not definitely disentangled. Some challenging hypothesis have been posed leading to specific management in order to mitigate the adverse effects.

This article is a review of the literature on the prevalence, pathophysiology and management of OBD and NBS.

KEYWORDS
Narcotic bowel syndrome; Opioid bowel dysfunction; Opioid; Pain; Constipation

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INTRODUCTION

Opioid bowel dysfunction (OBD)

Chronic pain is a worldwide medical challenge where one in five American and European adults have reported moderate-to-severe constant or alternating episodes of pain.[1] Opioids are the most influential drugs to lessen intense pain however their use is limited due to side effects.[2,3] Approximately 9 million people are annually affected by cancer–related pain for which opioids are the treatment of choice for these patients.[4-6] Opioid use has increased considerably, particularly in patients with cancer-related pain. Opioids detrimentally cause gastrointestinal symptoms such as dry mouth, constipation, straining, incomplete evacuation, nausea, vomiting, flatulence, bloating, increased gastric reflux, ileus, abdominal pain, lower abdominal discomfort, and in serious situations, fecal impaction with overflow diarrhea and incontinence, along with inadequate absorption of oral medications. These symptoms are collectively known as opioid bowel dysfunction (OBD) that impacts quality of life and performance status in consumers.[1,3,4,7-13] OBD has been initially described in the United States 20 years ago and 10 years ago in China.[11]

Additional adverse effects of opioids include depression of breath-

ing, clouding of consciousness, addiction, and tolerance.[14] The most common, intolerable symptom is constipation which is usually constant despite the use of laxatives.[1,4-6,15,16] On occasion, the constipation is attributed to an underlying disease that worsens with opioid therapy, thus becoming more complicated to control.[7] Constipation in patients with malignancies may be attributed to multiple factors such as diet, hydration, immobility, psychological factors, mechanical and metabolic effects of the tumor, and medications.[1]

Infrequently, patients may present with symptoms of diarrhea and bloating rather than constipation. This may be the result of the lactose content of popular opioid drugs and lactose intolerance in patients.[17]

Other potential factors include dosage, formulation, titration timetable, prior opioid consumption or multi-pharmaceutical. Codeine, amongst all opioid derivations has more association with OBD. Transdermal opioids such as fentanyl are known to cause less constipation compared to its oral or parental form.[6,7]

Narcotic bowel syndrome (NBS)

Narcotic bowel syndrome (NBS) is described as a subset of OBD defined by contradictory, chronic, recurrent, colicky and severe-to-very severe abdominal pain that occurs daily for more than 3 months and requires more than 100 mg of morphine equivalent per day for symptom relief. The key to its diagnosis is that the pain can be aggravated by continuing or increasing narcotic use to relieve pain, which results in a vicious pain cycle. First, the symptoms begin with tolerance or tachyphylaxis, followed by hyperalgesia even with increased opioid dose. Genetic or pharmacological factors can be related to the development of this syndrome. Physicians are mostly uninformed about this condition and continue with additional narcotics that result in extended hospitalization and readmission.[1,2,7,9,11,18-20]

Although pain is the predominant symptom of NBS, nausea, bloating, alternative vomiting, abdominal distension, and constipation are also common. The pain exacerbates when the narcotic effects wash out. During the time the pain-free course becomes more transient, acute decrease in the response to narcotics will occur which lead to increased narcotic use. Eventually this increase results in aggravation of gastrointestinal problems and lessens gut motility which lead to NBS. The symptoms can be provoked by eating - which can result in weight loss due to anorexia or sitophobia that is fear of eating due to the unpleasant symptoms like abdominal pain. These symptoms may correlate with delayed gastric emptying and intestinal transit. Fecal impaction and hemorrhoids may also be seen in these patients.

The correlation of symptoms with prolonged gastric emptying and intestinal transit is considerable. Laboratory tests are usually normal. A dynamic ileus or pseudo-obstruction can cause confusing evidence of partial intestinal obstruction as visualized by abdominal radiograph images.[2,6,7,9-11,21]

Abdominal pain is an inseparable symptom of IBS[22-24] along with numerous other disorders such as inflammatory bowel disease (IBD),[25] musculoskeletal and neuropathic pain,[6] and functional gastrointestinal disorders (FGID). Furthermore the prevalence of this syndrome shows an enhancement in the population due to increase in the use of opioids in non- malignant-related pains or dissonant behaviors but yet it has not been accurately estimated epidemiologically.[7,9,11]

It is estimated that 5%–13% of patients with IBD and 8% of the patients with IBS are chronic users of narcotics.[25] Psychiatric comorbidities such as depression and anxiety, a history of abuse, female gender, and clinical disease activity are also associated with narcotic consumption in patients with IBD.[25] IBS symptoms can also be seen in IBD patients at a frequency of 2-3 times more than healthy individuals. The overlap of these two disease may be a cause for chronic abdominal pain in IBD patients which leads to susceptibility for narcotic use.[20,25]

Although the use of narcotics for the above-mentioned illnesses should be restricted, however prescriptions are increasing.[11]

PATHOPHYSIOLOGY

Opioid bowel dysfunction (OBD)

The pathophysiology of OBD relies on effect of opioids on both central and peripheral mechanisms.[6,4]

δ,κ,μ are 3 major classes of CNS and peripheral opioid receptors that cooperate in opiate-induced deterrence of motor activity.[4,26] These receptors are members of seven transmembrane G-protein coupled receptors (GPCR) and are expressed by central and peripheral neurons, neuroendocrine (pituitary, adrenal), immune, and ectodermal cells, enteric neurons and intestinal muscle cells. These receptors can be stimulated by endogenous (endorphins, enkephalins, and dynorphins) and exogenous (morphine, codeine) agonists. Additionally there are other types of receptors (sigma, epsilon, orphanin) that are not considered to be classic opioid receptors.[4,6,7,14,16,27-29]

Inhibition of intestinal nerve, motor and secretory activities are the result of endogenous opioid use.[6] Opioids can directly affect the enteric nervous system which leads to alteration of intestinal fluid secretion.[10] In addition, opiates can cause intestinal muscle contraction by facilitation of acetylcholine release, reduction in nitric oxide discharge or directly by stimulation of opioid receptors.[7,13,26] Studies have shown that L-arginine, a precursor of nitric oxide, can reverse the effect of morphine in gastrointestinal motility in animal models.[30]

The release of opioid peptides in different classes of neurons in the myenteric and submucosal plexuses stimulates opioid receptors. This leads to regulation of the gastrointestinal system by influencing gut motility and secretion, which results in augmentation of sphincter tone, delayed gastric emptying, stimulation of motionless motor patterns and disruption of transmission within the enteric nerve pathways. These mechanisms plus deterrence of ion and fluid secretion lead to constipation.[7,26,31]

μ receptor is the main receptor that involves in pain management through CNS, gastrointestinal motility, secretion, absorption, and blood flow with in periphery. However OBD symptoms are attributed to delayed gastric emptying, gastrointestinal transit and colonic transit time, as well as inhibition of defecation that are interceded through peripheral opioid μ receptors.[4,6,7,15,27]

There are 3 subtypes of opioid μ receptors, μ-1, μ-2 and μ-3. The pain-relieving action of opioid μ-1 receptors applies spinal antinociception. Activation of opioid μ-1 receptors appears to be associated with smooth muscle contraction; opioid μ-3 receptors are present chiefly in endothelial cells that are correlated with production of nitric oxide which results in vasodilatation.[27,31]

A study 31 was performed to determine which subtype of opioid μ-receptors regulates intestinal tone. This study used loperamide as an agonist to provoke intestinal relax¬ation. As a result, activation of opioid μ-2 receptors due to the use of loperamide led to intestinal relaxation. The study showed that the associations of opioid μ-1 or μ-3 receptors with intestinal relaxation seemed to be doubtful.

Opioid μ-receptors that are expressed from myenteric neurons are mostly scattered throughout the small intestine and also located in the stomach and proximal colon. However constipation results from large bowel dysfunction. In one study prolonged gastrointestinal transit time of charcoal in mice that received loperamide and the entity of opioid μ receptors in the colon showed a possible role of opioid μ-2 receptors in opiate-induced constipation.[31]

Narcotic bowel syndrome (NBS)

There are three proposed mechanisms that contribute to augmentation of pain by prolonged use of opioids. First, the existence of a bimodal (excitatory and inhibitory) opioid regulation system in the dorsal horn where preferential activation of excitatory pathways over time may lead to opiate tolerance and pain augmentation. Second, descending facilitation of pain at the rostral ventral medulla and counter-regulatory mechanisms with release of anti-opioid neuromodulators such as dynorphin and cholecystokinin that oppose opioid antinociceptive function, and finally glial cell activation that contributes to morphine tolerance and boosts opiate-

induced pain.[11]

The molecular and neurobiological mechanisms of NBS are weakly understood and different hypotheses have been proposed that result in augmentation of pain experienced by an extended use of narcotics.

Recently a hypothesis has been developed regarding the role of CNS microglia and upregulation of neural signals by release of cytokines from inflammatory cells.[18]

TREATMENT

The European Association of Palliative Care Research Network (EAPC) has recommended a number of points for the prevention of adverse effects from opioid therapy that include reduction in the opioid dose, rotating opioids, changing the route of administration and symptomatic management. However these points have showed limited benefit for patients with OBD. Additionally, reduction in the opioid dose may lead to decreased analgesia.[6]

First step

Evaluation of the patient's medical history and life style that includes nutrition, physical activity and bowel function is necessary to determine adequate treatment. Management of OBD should not be limited to laxative use for constipation. Medical personnel have suggested non-pharmacological management that includes increasing dietary fiber intake, fluid consumption, physical activity, induction of daily bowel movements at the same time each day and preferably just after eating, and prevention or treatment of fecal impaction before starting the regimen. These proposals can assist in attaining an efficient result and may improve the quality of life in patients treated with opioids.[6,7,13]

Second step

The second step in OBD treatment involves management of nausea, vomiting, gastric reflux and constipation-related symptoms.[6] A prokinetic agent such as metoclopramide, dopamine antagonists or a serotonin antagonist which improves gastric motility can be used to relieve symptoms of nausea and/or vomiting, bloating, or early satiety that results from delayed gastric emptying, but it is believed to have little colonic effect.[6,7,13,27] Antacids, alginate preparations, low-dose histamine H_2-receptor antagonists and proton pump inhibitors are useful for mild, moderate and severe gastro-esophageal reflux.[6]

Other agents to be considered are neostigmine, an acetylcholinesterase inhibitor that can be administered for Ogilvie's syndrome of acute colonic pseudo-obstruction. Acetylcholine activates smooth muscle contractions and can cross opioid inhibitory modulatory effects, however its adverse effects include bradycardia and increased respiratory secretions. Cisapride is a 5HT4 agonist that increases gastric, small intestinal, and colonic motility. However, it is not available due to cardiac side effects. Tegaserod is a 5HT4 agonist that can boost peristalsis and can be used for chronic functional constipation and constipation-dominant IBS. Additional agents have been used for chronic functional constipation, but their function in opioid-induced bowel dysfunction is unknown. Misoprostol is a synthetic prostaglandin E1 analog that considerably reduces colonic transit time and enhances stool weight over a one-week period. Colchicine is used for chronic functional constipation. It decreases colonic transit time and increases the rate of bowel movements over four weeks Lubiprostone is a selective chloride channel (ClC-2) activator that can be used for chronic functional constipation. It is considered to raise fluid secretion that leads to an increase in the frequency of impulsive bowel movements.[27,32]

Third step

The third or main step is management of constipation by administration of laxatives or opioid antagonists.

Laxatives

Due to the effect of opioids on gastrointestinal motility, secretion, absorption, stool fluid content and consistency, laxatives may be used as prophylaxis or treatment for symptom relief.[6,7,32] Several

classes of laxatives are available. Selection of the appropriate laxative for each patient is dependent upon tolerability and side effects.

Most often, the combination of a stool softener (docusate sodium) and a stimulant laxative (bisacodyl or senna) is used to provoke colonic contractions. Stool softeners are commonly tolerated but if the patient's fluid consumption is insufficient or if is taken alone the stool softener will be insufficient.

Lactulose as an osmotic agent may be effective in many patients, but due to its requirement for high, repetitive daily doses it is inconvenient. Mild osmotic agents (e.g., 70% sorbitol solution, milk of magnesia), lubricant laxatives (mineral oil), a mild cathartic laxative (casanthrol), or a bulk-forming laxative are other types that can be used in patients who do not satisfactorily respond to treatment with a softening agent and/or stimulant.

Bulk-forming laxatives such as psyllium that consist of indigestible fibers affect patient symptoms by inducing a mechanical distention by magnetizing luminal water. It is contraindicated in patients with fluid restrictions, those bed ridden, patients with strictures or partial obstructions, and in other situations where adequate fluid consumption is required in order to prevent hard stool or intestinal obstruction.

Rectal laxatives, such as a bisacodyl suppository or enema are used to induce evacuation in more severe cases.[6,7,27,32]

Unless physicians are aware of the efficacy of laxatives as a key management in treating constipation, the opioid-mediated mechanisms of OBD may provide less amelioration of patient symptoms.[7]

Opioid antagonists

The first tertiary opioid antagonists that counteract the gastrointestinal effects of systemic opioids and both centrally and peripherally mediated opioid effects that have limited systemic absorption when administered orally are naloxone, naltrexone, and nalmefene.[4,5,7,16,27,32]

Limitations for use of these drugs are lack of selectivity for opioid-receptors in the gastrointestinal tract, lipid solubility, pharmacokinetic profiles, increase in plasma levels of unmetabolized naloxone, and the ability to infiltrate into the CNS which causes signs of withdrawal or diminution of analgesia even at doses less than necessary. All of these side effects require special consideration for dosing.[4,7]

Quaternary opioid antagonists, new class of drugs, are peripherally acting mu-opioid receptor Antagonists(PAM-ORAs) that consist of Methylnaltrexone(MNTX) and Alvimopan which are highly selective for the periphery. These drugs are derived from tertiary compounds with the addition of a methyl group that diminish the unwanted peripheral effects of opioids.[4,7,8,15,27,32] These agents are not absorbed systemically and do not cross the blood-brain barrier. The increase in polarity and decrease in lipid solubility compared to tertiary opioid receptor antagonists reduces their side effects on the CNS, therefore these agents can neutralize opioid-induced gastrointestinal effects, such as constipation delayed gastrointestinal transit and emesis, without affecting analgesia or accelerating withdrawal.[4,5,7,15,16,28,33]

MNTX can improve oral-cecal transit times even at high doses of opioid therapy without impacting the analgesic effect of morphine or causing withdrawal symptoms.[4,10,34] MNTX is prescribed every other day (seldom more than once every 24 hours) through subcutaneous injections to provoke bowel movements.[32]

Alvimopan is a peripherally acting opioid antagonist primarily used for postsurgical patients. Until now it has not been approved for opiate-induced constipation(OIC).[32,35] Studies have shown its effect on improvements in straining, stool consistency, incomplete evacuation, and abdominal bloating/discomfort.[35]

The result of two trials on the administration of prolonged-release(PR) oxycodone along with PR naloxone[36] and oral alvimopan versus placebo, once daily for 21 days, in patients with opioid-induced bowel dysfunction(OBD)[10] with equivalent analgesia showed significantly lessened severity of bowel dysfunction and opioid-induced constipation without any impact on analgesic effect. However the

improved bowel function was dose-dependent and the severity of opioid-induced constipation increasingly lessened with reduction of the oxycodone-naloxone ratio.[10,36]

A review of studies about combined prolonged–release oxycodone with prolonged–release naloxone (OXN) have shown efficient analgesia through restricted impact on gastrointestinal function, which makes OXN a practical agent for management of pain and opioid induced bowel dysfunction.[37]

Although laxatives change the normal function of the intestine in order to compensate for the effect of opioids, opioid receptor antagonists change it to normal function.[10]

A study of 168 patients with OBD showed that intravenous morphine considerably changed gastrointestinal transit time from 69 to 103 minutes, whereas administration of oral alvimopan overturned gastrointestinal dysfunction and kept transit time at its normal level without any change in pain intensity scores and pupillary constriction (an indicator of centrally mediated opioid effects).[10]

Other agents under investigation

New agents under investigation for OIC include naloxegol (previously identified as NKTR-118) which is a combination of oral naloxol (naloxone derivative) and a polyethylene glycol moiety; TD-1211, an oral multivalent inhibitor of the μ-opioid receptor; benvenopran(CB-5945, formerly ADL5945), another peripherally-acting μ-opioid receptor antagonist; prucalopride, a 5-HT4 agonist that accelerates colonic transit in both healthy individuals and in patients with functional constipation; and S-297995 (naldemedine), an oral, peripherally acting μ-opioid receptor antagonist.[35]

Narcotic bowel syndrome (NBS)

The best treatment for NBS is detoxification and systematic withdrawal with addition of treatments to diminish the withdrawal side effects and to supply analgesia that uses centrally targeted agents. The typical period needed for full detoxification is 10-14 days. First an equivalent dose of a medium-to-long acting opioid is replaced with the opiate, such as methadone, and subsequently the dose is decreased by 10%-33% per day until the patient is narcotic-free.

An antidepressant would be administered for pain management prior to opiate withdrawal and continued after withdrawal is completed. Examples include amitriptyline or duloxetine. Benzodiazepine (e.g., lorazepam) is prescribed to reduce anxiety during the withdrawal phase and is tapered off after opiate withdrawal is completed.

Oral clonidine (0.1 – 0.4 mg/day) has been administered after the narcotic dosage was reduced to about half to block withdrawal effects of long-term analgesia and antidiarrheal effect and titrated to maintain adequate blood pressure. It could be tapered or continued after withdrawal.[18,19,32]

Clonidine acts through stimulation of alpha-2 receptors in the locus coeruleus of the CNS and the gut wall. Management of NBS with clonidine leads to lessening of intestinal contractions and relaxation of the intestinal smooth muscle.[21,32,38]

Other treatments include specific treatment for constipation (e.g., PEG solution) or other agents mentioned above and psychological treatments that consist of cognitive behavioral therapy.[18,19]

Monitoring for orthostatic hypotension, syncope, urinary retention or cardiac dysrhythmias in rapid withdrawal regimens are used.[19]

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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