ORIGINAL ARTICLE

The opioid bowel syndrome: A review of pathophysiology and treatment

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ABSTRACT

Opioids are responsible for 25 percent of constipation in terminally ill patients. Patients in pain require prophylaxis to prevent opioid bowel syndrome (OBS). Laxatives are the treatment of choice, but are marginally effective. The development of quaternary opioid receptor antagonists is a step toward target-specific therapy for opioid-induced bowel dysfunction. This review will discuss the pathophysiology and management of OBS.

Key words: opioid bowel syndrome, pathophysiology, prophylaxis, bowel dysfunction

INTRODUCTION

Opioids have been used as antidiarrheals for centuries. The reasons for benefit are reduced intestinal propulsion, reduced transit, improved fluid absorption, reduced intestinal secretions, and prolonged mucosal contact time secondarily allowing absorption of bowel fluids.[1,2] On the other hand, opioids may cause opioid bowel syndrome (OBS) in individuals without diarrhea. OBS is associated with upper and lower abdominal symptoms—abdominal pain, bloating, colic, constipation, early satiety, nausea, and vomiting—and can mimic bowel obstruction.[1,2] Although OBS is frequently equated with constipation, and constipation remains the hallmark symptom, upper abdominal symptoms may be just as distressing to patients. If OBS remains untreated, anorexia, fecal impaction, inadequate absorption of medications, malabsorption of food, pseudo–bowel obstruction, and urinary incontinence will supervene.[1] Opioids will worsen and prolong postoperative ileus, which is also a type of OBS, because exogenous and endogenous opioids are one of the major factors contributing to prolonged hospitalizations and delayed recovery of bowel function postoperatively. Patients may limit opioids and forego pain relief to avoid constipation for fear of OBS. Many patients may, in fact, prefer poorly controlled pain and normal bowel habits to well-controlled pain and opioid-related gastrointestinal symptoms. Like other opioid-related side effects, OBS corresponds poorly to the opioid dose and there is no tolerance with time.[1,3]

Constipation occurs in more than 50 percent of patients on opioids and is five times greater in frequency than in the normal population.[3] Constipation is frequently underdiagnosed, and most physicians do not provide bowel prophylaxis for constipation when starting opioids.[3] Comedications such as anticholinergics, tricyclic antidepressants, selective serotonin reuptake inhibitors, and calcium-channel blockers add to the risk of constipation with opioids. Patients on opioids are frequently immobile and dehydrated, which further increases the risk for OBS. Recent surgery and gastrointestinal metastases also compound the risk.[3]

ASSESSMENT

The initial step to evaluating OBS is a history of associated symptoms followed by plain radiographs of the abdomen. An upright radiograph of the abdomen will detect air fluid levels consistent with a bowel obstruction and crucial to the differential diagnosis. Also, plain abdominal radiographs provide a means of scoring the severity of constipation (Table 1).[3]

PHYSIOLOGY AND PHARMACOLOGY OF THE GASTROINTESTINAL TRACT

Intestinal motility is dependent on the electrophysiological activity of smooth muscle, neural input from the central nervous system (CNS), and coordinated activity from the "gut" brain located within the myenteric plexus (between the outer longitudinal smooth muscle and the inner circular muscle). The submucosal neural plexus lies between the mucosa and circular muscle and coordinates motility absorption and secretion in conjunction with the myenteric plexus. Enteric neurohormones such as vasoactive intestinal peptide (VIP), secretin, neuropeptide Y, peptide YY, serotonin (5HT), acetylcholine, noradrenaline (NA), and endogenous opioids govern motility, secretion, and absorption. The extrinsic autonomic nervous

Table 1. Radiographic constipation score	
1 point	< 50 percent of stool in an abdominal quadrant
2 points	> 50 percent of bowel in a quadrant has stool
3 points	100 percent of the bowel within a quadrant has stool
Add the score for the four quadrants of the abdominal radiograph. If the score is ≥ 7 out of a possible 12 (4 × 3 points), then severe constipation is present.[3]	

system includes sympathetic and parasympathetic fibers that coordinate peristalsis, reflex motor activity, and secretory activity between the enteric nervous system (ENS) and the CNS.[1,2]

Smooth muscle normally has a continuous undulating electrical membrane depolarizing pattern.[4] Opioids have no effect on this undulating or rhythmic resting potential or slow-wave activity. Pacemaker cells called interstitial cells of Cajal govern the rate of undulating depolarization.[4] Electrical spikes from the ENS lead to smooth muscle contraction. Depolarization is initiated with luminal distension, which stretches the muscular wall, releases acetylcholine, and initiates longitudinal smooth muscle contraction. Smooth muscle is hyperpolarized by NA, which prevents smooth muscle contraction.[5,6] Myocytes of the stomach and small bowel contain gap junctions that pass electrical current from one cell to another, thus allowing a coordinated smooth muscle contraction.[5,6] A syncytial electrical oscillating contraction is due to these interconnections between long sheets of myocytes.[1] In counterdistinction, colonic myocytes lack gap junctions and fail to function as an intrinsic unit. Colonic contractions and motility are therefore more dependent on extrinsic neural input.[1]

The alimentary tract has three functional motor responses: long segment propulsion, short segment propulsion or segmentation, and nonpropulsion.[5-8] Propulsive movements require a coordinated contraction/relaxation response between longitudinal and circular muscle.[5-10] This coordinated movement is initiated with a bolus of food, which stretches the gut wall. The ENS then initiates a coordinated propulsive movement by contracting the proximal longitudinal muscle and relaxing the distal circular muscle. This is accomplished through activation of ascending excitatory cholinergic motor neurons, which innervate longitudinal smooth muscle, and simultaneous activation of inhibitory nitric oxide- and VIP-containing descending motor neurons, which innervate distal circular smooth muscle.[4,11,12]

The small bowel and the colon also produce regular segmenting contractions that are nonpropulsive and that mix food and digestive secretions.[1] In the colon, segmentation results in prolonged mucosal exposure and facilitates fluid absorption. During fasting and after feeding the stomach, the small bowel and colon have coordinated migrating motor complexes that sweep bowel contents distally, usually at 90-minute intervals.[1]

Enteric nervous system

The gut has as many neurons as the spinal cord. Between the two plexuses there are a complex array of neurons that are as complex in interaction and function as the neuronal structure of the spinal cord. There are submucosal intrinsic primary afferents, submucosal secretomotor neurons, myenteric intrinsic primary afferents, noncholinergic secretory and vasodilator neurons, excitatory circular muscle motor neurons, inhibitory circular muscle motor neurons, cholinergic secretomotor and vasodilator neurons, descending interneurons for secretomotor reflexes, descending interneurons for muscle motor reflexes, and migrating motor complexes.[1-3,5,6] A network of pacemaker cells, the interstitial cells of Cajal, along the myenteric and submucosal borders generates the rhythm of intestinal contraction, the loss of which causes idiopathic constipation and paraneoplastic pseudo-obstruction.[10] The ENS governs overall motility, secretion, blood flow, and gut-related immune function.

The brain-gut axis consists of cholinergic fibers derived from vagus and pelvic parasympathetics and NA-containing sympathetics from splanchnics derived from T5-L2 sympathetic paraspinal ganglion. Motor and secretory function is modulated centrally through the brainstem nucleus tractus solitarius and dorsal motor nucleus of the vagus. Sensory A delta and C sensory fibers travel, mostly with sympathetics, to govern visceral pain responses, and contain predominately κ opioid receptors.[10] Parasympathetics stimulate motility and secretion, whereas sympathetics do the opposite.

Neurohumeral mediators

Local and circulating neurohumeral factors govern motility and alter myoelectrical smooth muscle activity, muscle tone, bowel wall compliance, and intestinal transit (Table 2).[5] Hormones from the gut influence the ENS before and after meals. Plasma ghrelin released from the stomach increases gastric motility before meals and stimulates

Table 2. Influence of neurohumeral mediators on intestinal circular smooth muscle contraction[8]	
Stimulators	**Inhibitors**
Acetylcholine	GLP-1 glucagon-like peptide
Grehlin	Nitric oxide
Motilin	Noradrenaline
Opioids	Somatostatin
Prostaglandin E_2	Vasoactive intestinal peptide
Substance P	

neuropeptide Y release for appetite.[5-7] Postprandial endocrine responses include release of insulin, neurotensin, gastrin, glucagonlike peptides (GLP-1), and glucose-dependent insulinotropic polypeptides, which reduce motility and interrupt migratory motor complex frequency (Table 2).[5-7] VIP and nitric oxide are released from descending inhibitor motor neurons to inhibit circular muscle contraction, increase bowel compliance, and stimulate digestive secretions. Hormones regionally released by enterochromaffin cells—principally 5HT—reduce motility by activating enteric sensory neurons and vagal and intrinsic primary afferents, which in turn feed back on endocrine cells in an autoregulatory fashion.[5-7] Motor neuron excitation and contraction are stimulated by tachykinins and substance P, as well as acetylcholine, and in part by 5HT, which induces different responses depending on the receptors that are activated.[5-7] Peristalsis is governed by coordinating ascending cholinergic excitatory motorneurons, which stimulate longitudinal muscle to contract, and simultaneous activation of inhibitory noncholinergic nitric oxide—containing motor neurons, which prevents circular smooth muscle contraction (and increases bowel wall compliance). Ascending and descending motor neurons both contain opioid receptors.[6,9,10,12-14]

A neuroreflex occurs between primary intrinsic neurons of the submucosal plexus and mucosa, with integrating circuits within the myenteric and submucosal plexus, which control secretory responses. Noncholinergic neurons use substance P and VIP to stimulate secretions. Serotonin and NA released from enterochromaffin cells within the mucosa prevent primary intrinsic neurons from depolarizing cholinergic and VIP-containing neurons within the submucosal plexus and block fluid and chloride secretion.[5-7]

Serotonin plays a major role in initiating a diverse number of gastrointestinal responses, including nausea, vomiting, secretion, and peristalsis. In general, serotonin is prokinetic and prosecretory. There are 14 different 5HT receptors in the gut, however, three of which are known to be excitatory (5H2b, 5HT3, and 5HT4), and at least one of which is inhibitory (5HT1a). Serotonin responses may therefore be regionally different depending on the receptor subtype.[5,6]

OPIOID AGONISTS AND RECEPTORS

Opioid agonists and their receptors have a major influence on gut motility, visceral sensation, secretion, and absorption.[14-16] Enkephalins, β-endorphins, and dynorphin are found in enteric neurons in the myenteric and submucosal plexus and innervate smooth and circular and mucosal endocrine cells and immunocytes.[17] Opioid receptors μ, κ, and δ are found in high density in both plexuses, particularly in the gastric and upper small intestines. κ receptors are found predominately in the myenteric plexus, and μ receptors are abundant in the myenteric plexus and dominate the submucosal plexus.[17,18] There are species-specific differences in opioid receptor distribution, however.[9,12-14] For example, κ and μ receptors are found in neurons within the circular muscle, but κ receptors are selectively absent in longitudinal muscle.[13,18,19] The stomach and proximal colon have the greatest density of κ and μ receptors. The functional role of δ opioid receptors is relatively unknown.[20] Opioid receptors are not found on smooth muscle, but are located prejunctionally on various ENS neurons that innervate smooth muscle.[17,20] Within the gastric wall, μ and κ opioids cause circular smooth muscle contraction by blocking inhibitory ascending motor neurons, and μ receptors prevent longitudinal muscle contraction through preventing the release of acetylcholine from activating ascending motorneurons.[21-23] Opioids also block vagal firing in the brainstem through the nucleus tractis solatarius, leading to decreased autonomic output, which impairs gastric emptying.[24] Morphine increases gastric smooth muscle amplitude, but reduces the frequency of contraction and also peristalsis, leading to antral spasm and early satiety.[6,25,26] Opioids do not influence esophageal motility, but prevent relaxation of the lower esophageal sphincter, pylorus, ileocecal value, and rectal sphincter.[20] μ Agonists reduce gastric secretion by peripheral and central mechanisms.[27] Morphine increases serotonin release from submucosal neurons and serotonin binds to 5HT2 receptors, which in turn causes NA release. NA binds to α2 adrenoceptors on enterocytes and prevents secretion.[9,14,20,21,26,28-31]

The endogenous opioid system is a defense mechanism that modulates motility in the face of pathologic intestinal distention and inflammation. Exogenously administered opioids impair transit that is already slow, however, whether postoperatively or through medications, inflammation, sedentary existence, or dehydration. OBS is a combination of increased release of endogenous

opioids from enteric neurons, increased expression of enteric opioid receptors due to inflammation, and administration of exogenous opioids.[17,20]

Morphine prevents secretions stimulated by prostaglandin E2 and VIP2. This owes to morphine-induced release of serotonin from the submucosal and myenteric plexus. This is, again, a regional effect through 5HT1 or 5HT2 receptors, because systemic serotonin actually increases secretions. Chemical or mechanical sympathectomy abolishes the antisecretory effects of morphine.[2] Methylsergide blocks serotonin receptors, reverses the antisecretory effects of morphine, and impairs the increased absorption response caused by μ agonists.

OBS correlates best with opioid concentrations within the ENS, rather than plasma or CNS levels.[4] It was initially thought that increased fluid absorption from opioids was caused predominately by delayed intestinal transit, but it is now known that opioids directly suppress secretomotor neurons in the submucosal plexus and reduce secretion, as well as stimulate absorption independent of motility.[6]

POSTOPERATIVE ILEUS AND OPIOIDS

Postoperative ileus basically is a loss of coordinated motility and predominantly arises from colon dysmotility. Recovery of the small bowel occurs quickly, usually within 24 hours, and the stomach recovers between 24 to 48 hours, but the colon will not recover for 48 to 72 hours.[32] Postoperative paralytic ileus, therefore, by definition, is when ileus lasts more than three days.[32] Postoperative ileus is caused by increased sympathetic output from stress, by release of endogenous opioids as a result of intestinal manipulation during the operation, and by exogenous opioids. The duration of postoperative ileus is related to the degree of surgical trauma and is greatest after colonic surgery.[32]

Gut paralysis postoperatively is biphasic. The initial phase owes to release of enteric nitric oxide. Mucosal trauma then leads to infiltration of leukocytes and activation of endogenous macrophages. VIP, substance P, and calcitonin gene-related product are released locally due to trauma and inflammation. Cyclo-oxygenase 2 is upregulated in motor neurons, opioid receptors are expressed, and endogenous opioid peptides are released.[32] The result is smooth muscle paralysis and increased sensitivity to exogenous opioids.[11] Physical findings and the passing of gas or stool correlate poorly with the course of ileus, the normalization of intraluminal pressures, intestinal migration measured by radio-opaque markers, and normalization of ENS electrical activity.[1] Trials of postoperative nasogastric suctioning have not demonstrated benefits in accelerating the resolution of ileus because it does not treat the primary cause and may predispose individuals to atelectasis and pneumonia.[1] There are no data to substantiate the use of prokinetics in the management of postoperative ileus.[11,31,32] Early feeding leads to resolution of the ileus.[11,32] Epidural local anesthetics and opioid-sparing strategies using ketorolac for analgesia will reduce pain and postoperative ileus. The other option is the use of less-constipating opioids, such as tramadol, fentanyl, and buprenorphine, in substitution for morphine.[1] Recently, the use of peripheral-acting opioid-receptor blockers has significantly shortened the time to recovery and hospitalization.[18,20,33,34]

OPIOID BOWEL SYNDROME IN A NONSURGICAL PATIENT: NONPHARMACOLOGICAL MEASURES

At least three nonpharmacological approaches can be pursued to prevent or minimize OBS: 1) increased fluid intake, 2) exercise with frequent ambulation, and 3) promotion of a regular bowel habit.[1,3] Privacy is frequently neglected within the hospital, as rounds or radiographic studies occur at inopportune times. A respect for privacy may go a long way in promoting good bowel habits as well as dignity.[3]

LAXATIVES

Laxatives are bulk-forming agents, osmotics, surfactants, or stimulants. Laxatives increase fluid in the gut lumen, decrease fluid and electrolyte absorption, and increase motility of the upper gastrointestinal tract. Laxatives do not reverse opioid dismotility. The drawbacks to laxatives are that they increase the medication burden in those prone to nausea and are not "target specific" for opioid receptor-mediated side effects.[1]

In a series of 413 patients referred to palliative specialists and or daycare, 54 percent had constipation, 15 percent severely so.[35] One hundred sixty-five patients were using opioids at the time of referral, and 80 percent of these complained of constipation. Despite the use of stimulating laxatives and osmotic laxatives, 75 percent did not improve despite the fact that most were satisfied with the management of their constipation. There were no changes in constipation between users and nonusers of laxatives. Paradoxically, patients on strong opioids plus laxatives were more likely to be constipated than those on strong opioids alone, although this may be a selective bias. Nursing assessment poorly corresponded to patient grading of constipation severity. Only one out of five identified that a healthcare professional explained the rationale for laxatives.

In a prospective trial, laxatives were required in 87 percent of patients on potent opioids, but 64 percent of patients not on opioids also required laxatives.[36] Interestingly, opioids accounted for only 25 percent of constipation in terminally ill patients. Individuals varied widely in their sensitivity to laxatives. There did not

appear to be a fixed-dose relationship between laxatives and opioids. Stool frequency did not differ between patients on opioids and those not on opioids.[36] In summary, these two survey studies suggest that laxatives appear to be suboptimal in the management of OBS.

In randomized controlled trials of laxatives in the elderly, there is a nonsignificant trend in the number of stools per week and laxative use. Most trials were small, however, and lacked statistical power. There is no evidence that one laxative is better than another.[37-41]

Bulk laxatives

Bulk laxatives/softeners are nondigestible substances that increase fecal volume and (hopefully) stimulate a stretch reflex, thus initiating peristalsis. They are fermented in the colon, generating substances that stimulate colonic motility. Bulk agents work poorly in OBS, however, owing to the facts that peristalsis is already impaired and the distension reflex inhibited, bulk agents do not inhibit opioid-induced absorption. Intestinal secretions are inhibited by opioids such that bulk agents are desiccated within the bowel lumen. An additional 200 to 300 mL of water is necessary over and above the usual daily intake. Early satiety limits the tolerability of bulk agents. Bulk agents will not reverse severe opioid-induced constipation, but will promote constipation in dehydrated patients, and do not relieve opioid-induced upper gastrointestinal symptoms.[3]

Osmotic laxatives

Osmotic laxatives consist of magnesium salts or poorly digested carbohydrates. Magnesium salts work in the small and large bowel to promote peristalsis, whereas carbohydrates stimulate laxation through bacteria digestion in the colon. Fluid is drawn into the bowel by osmotic laxatives, which can be problematic in dehydrated patients. Magnesium salts interfere with absorption of medications, and should be avoided in renal failure.[3] In one study in terminally ill patients, 20 to 30 mL of lactulose was required twice daily to relieve constipation associated with opioids. Relief took three to four days, and less than one-half of the days were associated with a bowel movement while on lactulose. Twenty-one percent continued to have hard stools despite aggressive lactulose dosing.[42] To obtain a bowel movement, 60 mL or more of a carbohydrate laxative may be necessary. Sorbitol and lactulose produce the same laxation; however, sorbitol is less expensive and less nauseating.[37] Polyethylene glycol, compared to lactulose, produces less flatus and more stools in the short term. Twenty grams of polyethylene glycol is equivalent to 20 g of lactulose.[40,43,44]

Stimulating laxatives

Stimulating laxatives are anthraquinones (dantron, senna, or cascara) or diphenyl-methanes (bisacodyl, phenolphthalein). Stimulants encourage peristalsis in part through longitudinal muscle contraction and secondarily through inhibiting ATPase K^+ NA^+ activity (absorption). The bioavailability of most stimulating laxatives is 15 percent. Laxatives do not coordinate peristalsis, but stimulate muscle contraction and are not "target specific" for OBS. Colonic bacteria transform senna to an aglycone that gives senna its laxative properties. Long-term use of anthraquinones is known to damage neurons within the myenteric plexus, however. Colonic melanosis caused by anthraquinones is a result of apoptotic epithelial cells that are phagocytized by macrophages and remain within the mucosa.[3] There is not an advantage of one stimulating laxative over another or between stimulating laxatives or osmotic laxatives, although one early study suggested that osmotic laxatives worked better than stimulating laxatives. There are few randomized trials to guide choices or doses. Almost all recommendations are by expert opinion, however, because there are few randomized trials.[38]

Rectal measures in laxation

One-third of patients require rectal measures for laxation. Suppositories, enemas, and manual disempaction are required in those with dysphagia, those who are nauseated, or those who have a bowel obstruction. Suppositories work by causing reflex emptying through rectal distension.[3] Glycerol suppositories also act as a lubricant. Bisacodyl suppositories have a dual action of mechanical and chemical colonic stimulation. Enemas are used only as rescue measures. A "mini enema" (60 cc) and larger-volume phosphate enema of 130 mL have similar benefits. Mini enemas should be used only when soft stool is present in the rectum.[3] High-volume enemas and manual disempaction are needed for fecal impaction. Enemas using cottonseed oil, paraffin, or mineral oil soften hard stool and will help relieve a hard impaction. Saline or oil enemas should be delivered at the highest descending point in the rectum above the impaction, to wash the impaction downstream, and not in the rectum or anus, below the impaction. Failure to disempact is as much a technical failure as a failure of the enema, per se.[3]

MISCELLANEOUS NONSPECIFIC THERAPY

Colchicine, used for acute gout, causes diarrhea as a side effect that can be beneficially used to relieve chronic constipation. There are no trials of colchicine in OBS. Prokinetics such as erythromycin, domperidone, cisapride, and metoclopramide have been used for OBS.[31] Erythromycin stimulates upper gastrointestinal motilin

Table 3. Less-constipating opioids
Tramadol
Buprenorphine
Fentanyl
Methadone

receptors, but is unlikely to produce a colonic action. Metoclopramide has been successfully used as a continuous infusion but can cause extrapyramidal side effects.[3] Cisapride (not commercially available) and erythromycin can both cause ventricular arrhythmias, particularly when combined with medications that inhibit CYP3A4. Misoprostol, a synthetic prostaglandin used to reduce the risk of gastric ulcers associated with nonsteroidal anti-inflammatory medications, causes diarrhea. Misoprostal is expensive, however, and untried in OBS. Finally, clonidine has been successfully used to treat OBS in a case report.[45]

OPIOID ROTATION AND OPIOID SPARING

Intractable OBS while on morphine may be an indication for opioid rotation. Morphine concentrates within the intestinal lumen and intestinal smooth muscle. Other opioids, such as methadone and fentanyl, are less constipating.[46] Buprenorphine is the least-constipating opioid, with it occurring in only 5 percent of treated patients (Table 3).[47] Adding ketorolac to morphine may reduce opioid doses and facilitate laxation.[48-51]

OPIOID RECEPTOR ANTAGONISTS

Opioid receptor antagonists are target-specific therapy for OBS. There are two types of antagonists: poorly absorbed oral opioid antagonists, and peripherally restricted μ opioid antagonists.[1,3]

Poorly absorbed opioid antagonists

Naloxone, a lipid-soluble tertiary multiple-receptor opioid antagonist, has an oral bioavailability of 2 to 3 percent owing to extensive hepatic first-pass clearance.[1,8,9] Absorption is increased with dose, however, and so naloxone has a narrow therapeutic index.[1,8,9] Doses of 0.4 to 4.0 mg daily by mouth are ineffective; doses of 8 to 12 mg reverse OBS, but can precipitate systemic withdrawal.[8] Initial doses should be 5 mg daily to avoid precipitating opioid withdrawal. The usual doses are 8 to 10 mg daily, up to 10 to 20 percent of the total daily morphine dose, or a dose equivalent to the four-hour dose.[3,8] In randomized controlled trials 10 percent of the morphine dose was used, but in open trials doses up to 20 percent of the total oral morphine equivalent were used. Some patients developed withdrawal symptoms and resurgence of pain with oral naloxone titration.[52] More than one-half of patients will have laxation with oral naloxone. Dosing based on the opioid dose may not be correct. Constipation from opioids is poorly related to opioid dose. Patients who have been on long-term opioids are more sensitive to opioid withdrawal when treated with oral naloxone than those on short-term opioids.[8] The risk of withdrawal will be greater on higher doses of opioids if naloxone dosing is based on a percentage of the daily opioid dose. Gastrointestinal opioid receptors may be completely bound before adequate analgesia (and CNS levels), and a "ceiling effect" on dose-constipation effects thus may occur. Approximately 10 to 15 percent of opioid analgesia is lost with the use of oral naloxone.[8,53,54]

Nalmephene is an active, long-acting antagonist derived from naltrexone. Glucuronide derivatives of nalmephene have been developed to reduce OBS in those on methadone maintenance therapy.[55] It is thought that glucuronide metabolites are poorly absorbed and, thus, will not reduce analgesia or precipitate withdrawal. Colonic bacteria contain β-glucuronidase, which liberates nalmephene from its glucuronide side chains and allows nalmephrene to interact with opioid receptors in the colon and antagonize opioid-induced constipation. Nalmephene is also absorbed systemically through the colonic wall, and precipitates an abstinence syndrome in opioid maintenance therapy.[55]

Peripherally restricted opioid antagonists

Peripherally restricted opioid receptor antagonists are polar, less lipid soluble, and quaternary in structure, which restricts them from crossing the blood-brain barrier.[8] Both quaternary opioid antagonists in development, methylnaltrexone and alvimopan, may be given orally or parenterally without reversing analgesia. Both have the potential of producing laxation within hours, and both may relieve upper and lower gastrointestinal symptoms related to OBS.

Methylnaltrexone. Methylnaltrexone improves orocecal transit time in a dose-dependent manner in normal volunteers given parenteral morphine. Transit time decreased from 155 ± 27.9 minutes to 110 ± 41.0 minutes with 0.1 mg per kg of parenteral methylnaltrexone and from 140 ± 88 minutes to 108 ± 60 minutes with 0.3 mg per kg of parenteral methylnaltrexone.[56] Methylnaltrexone may also reverse opioid-induced nausea, pruritus, and flushing.[57] A methylnaltrexone dose of 0.45 mg per kg will prevent 97 percent of morphine-induced orocecal transit time; 0.3 and 0.1 mg per kg subcutaneous prevented 77 percent and 64 percent of morphine-induced transit time, respectively.[58]

Patients on methadone maintenance therapy and with

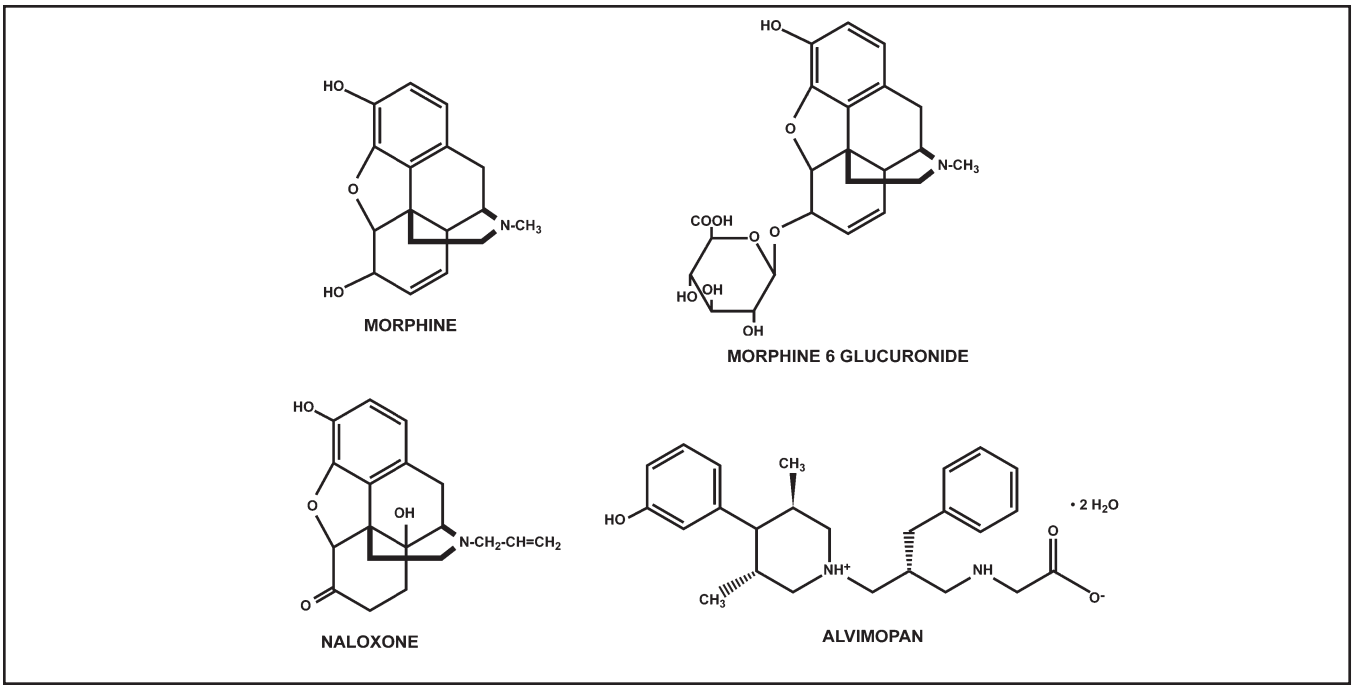

Figure 1. Molecular structures of morphine, morphine-6 glucuronide, naloxone, and alvimopan.

constipation (defined as one to two stools per week) respond with immediate laxation to methylnaltrexone doses of 0.35 to 0.45 mg per kg given intravenously twice daily. Orocecal transit time was reduced from 150 minutes to 60 to 90 minutes by the methylnaltrexone. Abdominal cramps were experienced particularly at the higher doses, but withdrawal did not occur. Both methadone maintenance therapy and chronic opioids for cancer pain increase sensitivity to methylnaltrexone, and lower doses (i.e., 0.1 mg per kg) should be used.[55,59]

In a randomized blinded trial, oral methylnaltrexone in doses of 1 and 3 mg per kg produced immediate laxation in individuals on oral methadone maintenance therapy who had significant constipation. Mild abdominal cramps were experienced by most, but systemic withdrawal symptoms did not occur.[60]

Oral bioavailability of methylnaltrexone is less than 1 percent; however, absorption is individually variable.[7,61,62] Laxation is not related to plasma level. The dose equivalents when converting from oral to subcutaneous are by a factor of 100.[56] Peak free methylnaltrexone is significantly less when given subcutaneously as compared to intravenously. An intravenous dose of 0.08 mg per kg is equivalent to a subcutaneous dose of 0.1 mg per kg. The time to maximum levels is 16 to 20 minutes for subcutaneous injection and is shorter for intravenous administration. The half-life is two hours. Clearance of methylnaltrexone is independent of route of administration.[56]

Alvimopan. Alvimopan is a potent μ opioid receptor antagonist (Figure 1). The inhibitor constant (Ki) is fourfold lower than naloxone demonstrating a greater affinity (and inhibition) to the μ receptor. Alvimopan also binds with a lesser affinity (inhibition) to κ and δ opioid receptors.[34]

Alvimopan, in a phase I study, completely prevented loperamide-induced changes in gastrointestinal transit in normal volunteers. Doses ranged from 2.4 to 24.0 mg by mouth.[34] Additional studies in normal volunteers found that 4 mg of alvimopan normalized orocecal transit when given with morphine 0.05 mg per kg. Oral alvimopan 3 mg three times daily reversed the delayed lower gastrointestinal transit caused by oral morphine 30 mg twice daily.[34,63-65] In phase II trials there is a dose-dependent increase in the number of bowel movements, stool weight, reduced hard stools, and need to strain.[34]

In a randomized controlled trial of alvimopan 0.5 mg and 1.0 mg compared to placebo, alvimopan increased the number of stools, reduced the time to first bowel movement, and improved patient satisfaction compared to placebo in patients on chronic opioids. Eleven percent discontinued alvimopan due to cramps, nausea, vomiting, diarrhea, and flatulence. Two of 105 had worsening pain on alvimopan.[66] Alvimopan has also been tested in the management of postoperative ileus. Two randomized trials have demonstrated that 6 and 12 mg of oral alvimopan improve time to gastrointestinal recovery and decrease the time in hospital compared to placebo.[33,67]

Oral bioavailability of alvimopan is 6 percent.[18] Metabolites of alvimopan are derived from gut flora rather than hepatic metabolism. There is no evidence that alvimopan is metabolized by cytochrome P450 metabolism

or by glucuronidation. The time to maximum plasma concentrations for oral dosing is 1.5 to 3.0 hours, and the half-life is 1.3 hours for a 12-mg dose. The half-life of intravenous alvimopan is 10 minutes. Alvimopan does not accumulate with repeat dosing.[18]

SUMMARY

OBS is almost inevitable for patients on potent opioids who do not receive prophylactic laxatives. There is no one right laxative program, and most guidelines are by expert opinion. All laxatives have drawbacks regarding efficacy and toxicity. Target-specific opioid receptor antagonists are either opioid antagonists with high first-pass hepatic clearance or quaternary opioid antagonists that do not cross the blood-brain barrier. Both classes of opioid antagonists have clinical use, although naloxone has a narrower therapeutic index. Both classes of peripherally limited opioid receptor anatagonists have advantages over laxatives in specificity and onset to laxation and may relieve upper abdominal symptoms. Both quaternary opioid antagonists are ideal for prophylaxis. Further research is necessary to clarify clinical use. Cost and versatility will also be a major factor for routine use.

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