Methylnaltrexone for the management of unwanted peripheral opioid effects

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For many a patient suffering from moderate to severe pain, opioid analgesics offer the anxiously sought-after relief, but at a high price. While the pain is wearing off, distressful constipation, abdominal discomfort, nausea and urinary retention ensue. These unwanted effects have been difficult to deal with, and the laxatives that are usually prescribed ameliorate constipation in no more than 50% of the patients receiving opiates. A new treatment concept emerged from the development of opioid receptor antagonists with a peripherally restricted site of action. One of these treatments is methylnaltrexone, which clinical trials have shown to be of benefit in opioid-induced constipation, postoperative ileus and urinary retention, while analgesia remains unabated. The drug is well tolerated and holds great promise in freeing opioid therapy of some of its most-feared adverse aspects. In 2008, methylnaltrexone (Relistor™) was approved in the USA, Canada and Europe for the treatment of opioid-induced constipation in patients with advanced illness.

Keywords: constipation, methylnaltrexone, opioid analgesics, opioid-induced bowel dysfunction, opioid-induced urinary retention, peripherally restricted opioid receptor antagonists, postoperative ileus

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Opioids denominate exogenous and endogenous compounds that activate the principal μ-, κ- and δ-opioid receptors. The term opioid has been derived from opium, which refers to the dried latex collected from the unripe seed capsules of *Papaver somniferum*. Due to its efficacy, opium has been used since ancient times to treat pain and diarrhea – the major opioid alkaloids being morphine and codeine. Despite many attempts to develop other strong pain medications, opioid analgesics have remained the mainstay of therapy in many patients with moderate to severe pain. Unfortunately, adverse effects can severely compromise the therapeutic benefit offered by these drugs [1]. In the periphery, these unwanted effects of opioids comprise gastrointestinal (GI) stasis, urinary retention and pruritus, and can be disabling to a degree that opioid treatment needs to be reduced or even abandoned.

Opioid-induced bowel dysfunction, prolongation of postoperative ileus & urinary retention

In the GI tract, the adverse effects of opioids manifest themselves primarily in constipation, characterized by a reduction of defecation frequency, hard, dry stools, fecal impaction, incomplete evacuation, defecation-associated straining, abdominal bloating and distention, abdominal discomfort and pain, and increased gastroesophageal reflux. Collectively, these symptoms are embodied in the term opioid-induced bowel dysfunction (OBD), which may lead to secondary complications such as pseudo-obstruction of the bowel, anorexia, nausea and vomiting, as well as interference with oral drug administration and absorption [1,2]. The symptoms associated with OBD can profoundly impair the quality of life, and in some patients can be so severe that they prefer to discontinue analgesic therapy rather than experience the discomfort of OBD [1,3]. Unlike other adverse effects of chronic opioid therapy, such as sedation, nausea and vomiting, which often resolve with continued use, OBD generally persists throughout treatment [1].

The distressing nature of OBD is underscored by the frequency of its occurrence. Since GI function is impaired by subanalgesic opioid doses, OBD affects 40–90% of patients taking opioids for chronic pain [1,4]. There are data in the literature that indicate that the distress of OBD can rival that of pain associated with the underlying disease [1].

Although less well studied, urinary retention owing to impaired micturition is another side effect of opioid therapy, and a significant source of morbidity. Studies in postoperative patients indicate that total urinary retention requiring catheterization may develop in 3.8–18.1% of the patients, the use of patient-controlled analgesia with morphine being a significant risk factor [4,5]. Partial urinary retention is thought to be an even more frequent adverse reaction to opioid therapy.

Another unwanted condition related to opioid medication is postoperative ileus (POI), which occurs most commonly following abdominal or pelvic surgery. POI is characterized by bowel

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distention, lack of bowel sounds, accumulation of gas and fluid in the GI lumen, intolerance of solid food, nausea, vomiting and delayed passage of flatus and stool [1,6,7]. Motor stasis occurs in all segments of the digestive tract, the colon usually being most severely affected, and lasts on average 3–7 days [4]. Opioid analgesics have an adverse influence on postoperative GI motility, as their use for postoperative analgesia delays recovery of normal bowel function [1,4].

Mechanisms of action of opioid-induced inhibition of GI function & micturition

The effect of opioid analgesics on the GI tract is thought to reflect the action of endogenous opioid peptides on GI physiology. Both endogenous and exogenous opioids modify GI function by interaction with μ-, κ- and δ-opioid receptors, all of which are present in the enteric nervous system [8–11]. Opioid receptor agonists can interrupt both excitatory and inhibitory enteric pathways governing muscle activity [2,11]. For this reason, the net effect on motility can be quite diverse. Suppression of excitatory neural pathways results in suppression of acetylcholine release and peristaltic contractions, whereas blockade of inhibitory neural pathways results in depression of nitric oxide release from inhibitory motor neurons, disinhibition of GI muscle activity, elevation of resting muscle tone and nonpropulsive motility patterns [2,9,11–13].

Depending on whether interruption of excitatory or inhibitory neural pathways is prevailing, muscle relaxation or spasm will ensue in response to opiate administration. As a result, opioid receptor agonists inhibit gastric emptying, increase pyloric muscle tone, induce pyloric and duodenojejunal phasic pressure activity, disturb the migrating myoelectrical complex, delay transit through the small and large intestine and elevate the resting anal sphincter pressure [1,2,11]. The halt in propulsive motility combines with inhibition of GI ion and fluid transport. Through prolonged contact of the intestinal contents with the mucosa and interruption of prosecretory enteric reflexes, opioids attenuate the secretion of electrolytes and water, and facilitate the net absorption of fluid [12,14,15]. The patient experiences constipation, hard, dry stools and abdominal discomfort.

In considering pharmacological opportunities to manage OBD, it is important to know the opioid receptor subtypes responsible for this condition. Opioid receptors belong to the family of metabotropic membrane receptors that couple via the G_i/G_o subtypes of G-proteins to various cellular transduction processes [10,11]. Studies in isolated tissues from the human intestine show that μ-, κ- and δ-opioid receptors contribute to opiate-induced inhibition of muscle activity [1,2]. Propulsive motility in the rat intestine is blocked by μ- and δ-opioid receptor agonists [12], whereas peristalsis in the guinea-pig intestine is suppressed by activation of μ- and κ-opioid receptors [16]. Although these data indicate that OBD is mediated by opioid receptors in the gut [1,2], there are experimental data to show that intracerebral injection of opioid analgesics also delays intestinal transit [17]. However, opiate-induced blockade of gut motility correlates better with opiate concentrations in the gut than with opiate concentrations in the brain [18]. In addition, the *N*-methyl quaternary analogs of naloxone and naltrexone, which do not cross the blood–brain barrier, are able to fully antagonize the effects of morphine in the canine and rat intestine [1,18]. It follows that the adverse influence of opiates on GI function results primarily from interaction with opioid receptors in the gut.

The pathophysiology of prolonged POI involves inflammatory, immunological, muscular and neurogenic mechanisms [7,19,20]. Postoperative pain control with opioids is thought to exacerbate POI, as the time required for resolution of POI following colectomy is related to the dose of morphine administered [21]. In addition, it is assumed that the GI opioid system contributes to the condition [2,8].

The pathophysiology of opioid-induced urinary retention is not completely understood. Opioids decrease the force of detrusor contraction, decrease the sensation of bladder filling, but probably do not increase sphincter tone [22]. These adverse effects involve opioid actions in the CNS and, possibly, in the periphery [23–25].

Unmet needs in the current management of unwanted opioid effects in the periphery

The frequency and distress of OBD profoundly impairs the quality of life, and often necessitates rescue treatment, which is difficult to achieve. There are two main approaches to the pharmacological management of OBD: nonspecific treatment with laxatives, and specific treatment with opioid receptor antagonists (**Box 1**).

Softening, stimulant and osmotic laxatives are most commonly used to ameliorate OBD, and treatment attempts with prokinetic drugs have also been made [1,3,6,26]. Unfortunately, only

Box 1. Nonspecific and specific treatment of unwanted effects of opioids in the periphery.

Nonspecific treatment of opioid-induced bowel dysfunction

Drugs without affinity for opioid receptors

- Drug classes
  - Laxatives
  - Prokinetic drugs
  - Opioid-sparing regimen
- Unsatisfactory control of opioid-induced constipation

Specific treatment of opioid-induced bowel dysfunction

Opioid receptor antagonists with limited intestinal absorption

- Drugs
  - Oral naloxone
- Prevention of opioid-induced constipation

Peripherally restricted opioid receptor antagonists

- Drugs
  - Parenteral and oral methylnaltrexone
  - Oral alvimopan
- Prevention of opioid-induced constipation
- Shortening of postoperative ileus
- Attenuation of opioid-induced urinary retention
- Attenuation of opioid-induced pruritus

approximately 50% of the patients treated with laxatives experience relief from OBD [3,27]. Due to the limited efficacy, rescue treatment requires frequent dose adjustments, combination therapy and laxative switching [3,6,27]. For this reason, many opioid-sparing regimens have been tested, including transdermal administration of opiates [1,28], but none of these attempts have solved the problem of OBD in a satisfactory manner. Apart from catheterization, the treatment options for opioid-induced urinary retention are likewise limited [25].

Proactive management of POI includes the use of epidural anesthesia and analgesia, laparoscopic instead of open-abdominal surgery, early nasogastric tube removal, early oral nutrition and early ambulation following surgery [1,6,7,29]. This polymodal fast-track postoperative management can be combined with the use of laxatives and prokinetic drugs to accelerate recovery of GI function [1,7,30,31]. However, the therapeutic value of these medications in the relief of POI with or without opiate use remains largely unsubstantiated [1]. Among all available treatment options, epidural local anesthesia appears to be the most efficacious method for relieving pain and shortening POI [1].

Specific treatment of unwanted opioid effects in the periphery

The primary objective in the management of OBD is to prevent GI symptoms, rather than treat established motor stasis [1,2]. Since opioid-induced analgesia is primarily mediated by μ-opioid receptors in the CNS, the rational approach to prevent OBD would be to combine opioid analgesics with opioid receptor antagonists that cannot penetrate the blood–brain barrier. As a result, the adverse effects of opioid analgesics in the periphery would be avoided, whereas their central analgesic action would be preserved. This approach has been validated by the use of opioid receptor antagonists with limited systemic absorption, and by the development of peripherally restricted opioid receptor antagonists [1,2,4,32].

Opioid receptor antagonists with limited systemic absorption

Naloxone is a pan-opioid receptor antagonist [33] with an oral bioavailability as low as 2% due to extensive first-pass metabolism. Consequently, oral naloxone has been found to reduce constipation, but not pain caused by morphine in rats [34]. These observations have been confirmed in clinical studies in which oral naloxone turned out to improve OBD without necessarily compromising opiate-induced analgesia [35–37]. Once it has passed the liver, however, naloxone can easily enter the brain and reverse opioid-induced analgesia [1]. Thus, the therapeutic range of naloxone is rather narrow because of the need to titrate peripherally versus centrally active doses [35]. Despite this limitation, a combination of oral oxycodone and naloxone at the weight ratio of 2:1 has been licensed in Germany and, being formulated as a prolonged-release preparation, has been shown to have analgesic efficacy at a low rate of OBD [38].

Peripherally restricted opioid receptor antagonists

Quaternary analogs of opioid receptor antagonists such as naloxone and naltrexone display a pharmacokinetic profile of limited absorption from the gut and inability to enter the brain [1,6]. As a consequence, these compounds antagonize the effects of morphine in the periphery at doses that are devoid of effects on the CNS [39]. Like methylnaltrexone, alvimopan is a μ-opioid receptor-preferring antagonist, which, owing to its polar structure, exhibits low systemic absorption and a limited ability to enter the brain [2,4,40,41]. Since it is rapidly degraded after intravenous injection, alvimopan is formulated for oral intake, in which case it potently blocks μ-opioid receptors in the gut with a prolonged

duration of action. Preclinical and Phase I studies have established the pharmacokinetics, safety, efficacy and selectivity of alvimopan in its antagonism of peripheral opioid receptors [1,2,4,40,41]. In these studies, alvimopan was found to prevent opioid receptor agonists from delaying GI transit in healthy subjects without antagonizing central opioid effects, such as analgesia and pupillary constriction [40–42].

Several Phase II and III trials attest to the utility of alvimopan in treating OBD and POI [2,5,40,41,43–46]. In patients on chronic opioid therapy for non-malignant pain, alvimopan (0.5 or 1 mg twice daily for 6 weeks) is able to increase spontaneous bowel movements during the initial 3 weeks of treatment and improve other symptoms of OBD over the whole treatment period, while analgesia is not compromised [41,44]. Four Phase III trials conducted in North America have shown that alvimopan (6 or 12 mg twice daily) accelerates GI recovery and shortens the duration of hospitalization after abdominal or pelvic surgery, whereas an international Phase III trial failed to reveal a significant effect of alvimopan on POI unless subjects were maintained on intravenous patient-controlled opioid analgesia [41,45–47]. The variability in the efficacy of alvimopan may, in part, be due to differences in pharmacokinetics and dosing, as the rate of alvimopan absorption is slowed in surgical patients [48].

Studies addressing the acute (up to 6 weeks) safety of alvimopan in patients with OBD have shown that the drug is well tolerated, the adverse effects being primarily gut-related and including nausea, vomiting and abdominal discomfort [40,41,43,44,47]. However, the long-term safety of alvimopan remains to be established, given that a 1-year Phase III trial of patients receiving opiate therapy for chronic noncancer pain revealed a numerical imbalance in the number of ischemic cardiovascular events, neoplasms and fractures in patients receiving alvimopan (0.5 mg perorally twice daily), relative to placebo [41,101]. A 2-year carcinogenicity study in mice and rats showed that oral alvimopan significantly increased the incidence of cutaneous/subcutaneous fibroma, fibrosarcoma and sarcoma, and osteoma/osteosarcoma in female mice [101]. In May, 2008, alvimopan (Entereg™) was approved by the US FDA for the treatment of POI following bowel resection in hospitalized patients aged 18 years or older. The recommended dosing is 12 mg just before surgery, and 12 mg twice daily post-surgery for up to 7 days [102].

Methylnaltrexone

Methylnaltrexone (Relistor™) was among the first quaternary derivatives of opioid receptor antagonists that were shown to antagonize peripheral, but not central, effects of morphine [39]. This property was subsequently confirmed in humans, and the compound was scheduled for clinical development. The available study results attribute methylnaltrexone efficacy and safety in managing the peripheral side effects of opioid analgesics, at least in the short term.

Chemistry

Methylnaltrexone is obtained by attaching a methyl group to the amine configuration in naltrexone (**Figure 1**). The positively charged quaternary configuration increases the polarity and reduces the lipid solubility of the compound, relative to naltrexone [49]. Used as a bromide salt, methylnaltrexone is a white, odorless powder that is freely soluble in water. For clinical trials, the compound has been formulated both as a solution for infusion or injection, and as capsules or tablets for oral intake [49].

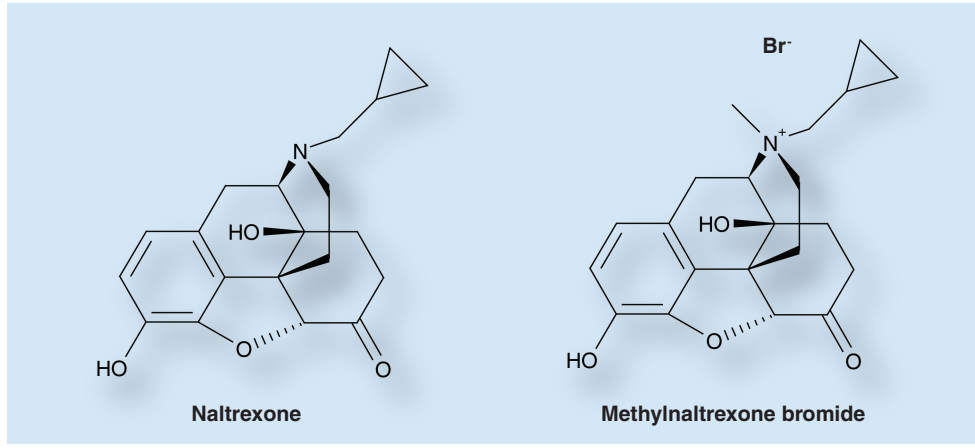
Pharmacodynamics

Methylnaltrexone is a μ-opioid receptor-preferring antagonist, exhibiting a half-maximal inhibitory concentration (IC_{50}) of 70 nM at human μ-opioid receptors [49]. It has a reduced affinity for κ-opioid receptors and considerably less affinity for δ-opioid receptors, although the data in this respect are somewhat conflicting [49–51]. Basically categorized as a pure antagonist [49], methylnaltrexone has some agonist activity at heterologously expressed μ-opioid receptors [50]. Preclinical studies have confirmed that methylnaltrexone antagonizes the action of μ-opioid receptor agonists to inhibit GI transit and evoke emesis [49–51].

Pharmacokinetics & metabolism

Owing to its quaternary structure, methylnaltrexone exhibits low oral bioavailability and does not cross the blood–brain barrier [3,49,50]. Its ability to prevent the undesired effects of opioids in the periphery without interfering with opioid actions in the brain has been substantiated in preclinical and clinical studies [49,51]. Whereas in dogs and humans methylnaltrexone prevents the adverse effect of opioid analgesics on GI function without attenuation of analgesia, analgesia in rats is appreciably compromised [3]. This species dependence of the peripheral selectivity of methylnaltrexone arises from its demethylation

Figure 1. Naltrexone and methylnaltrexone bromide.



to naltrexone, which readily penetrates the blood–brain barrier: demethylation occurs in mice and rats, but is negligible in dogs and humans [3,52].

While readily bioavailable after parenteral administration, methylnaltrexone is absorbed from the GI tract only to a limited extent [53]. The plasma levels of methylnaltrexone are even lower when the drug is administered orally as an enteric-coated formulation, although enteric-coated methylnaltrexone is more efficient in preventing morphine-induced retardation of orocecal transit time than the uncoated preparation [54]. Thus, reduced oral bioavailability is associated with enhanced efficacy, which suggests that oral methylnaltrexone acts locally in the gut to reverse morphine-induced motor stasis.

Following parenteral injection of methylnaltrexone 0.3–0.45 mg/kg, the time to maximum plasma concentration is approximately 20 min, the elimination half-life in blood plasma is approximately 1.5–3 h, and the terminal half-life is approximately 6–9 h [49,51,55]. Repeated intravenous administration of 0.3 mg/kg doses at 6-h intervals does not result in accumulation of the drug [56], and metabolism of methylnaltrexone does not play a major role in its predominantly renal route of elimination [49,51].

Clinical efficacy

The therapeutic and safety profile of methylnaltrexone has been evaluated in several Phase I, II and III trials (**Table 1**). In healthy volunteers, both the parenteral and oral formulations, as well as single and repeated dosage regimens, were found to be efficacious in preventing the morphine-induced prolongation of gastric emptying and orocecal transit time without significantly attenuating morphine-induced analgesia [53,54,56–60].

Double-blind, randomized and placebo-controlled Phase II studies proved that methylnaltrexone is capable of relieving constipation in methadone-maintained, opioid-dependent volunteers (**Table 1**). Intravenous methylnaltrexone shortens the orocecal transit time and causes laxation associated with mild abdominal cramping, but does not elicit any sign of opioid withdrawal [61]. Compared with placebo, oral methylnaltrexone is likewise able to provoke laxation in methadone-maintained patients without precipitating opioid withdrawal in any subject [62]. However, the latency to the first bowel movement is significantly longer following oral intake of the drug than after intravenous administration. The doses of methylnaltrexone required to induce bowel movements in subjects on chronic methadone were lower than those required in subjects who were not opioid dependent.

The utility of subcutaneous methylnaltrexone to selectively counteract opiate-induced stasis in the GI tract has been proven in Phase II and III studies of patients with advanced illness requiring high doses of opiates for pain control (**Table 1**). The efficacy and dose–response relationship of methylnaltrexone in relieving opioid-induced constipation was first evaluated in a multicenter, randomized and parallel-group Phase II trial involving 33 adult patients with advanced illness (terminal or end-stage diseases such as metastatic cancer and AIDS) who were receiving chronic opioid therapy for pain on a daily basis [63]. Patients were eligible for the study if they had no bowel movements for 2 days, even if they received

Table 1. Overview of fully or partially published clinical trials of methylnaltrexone in opioid-induced bowel dysfunction, opioid-induced urinary retention and postoperative ileus associated with opiate medication.

Dose and route of administration	Type of trial	Major outcome from the use of methylnaltrexone	Ref.
0.64, 0.7, 2.1, 6.4 or 19.2 mg/kg p.o.	Phase I	Efficacy and safety in preventing OBD	[53]
3.2 or 6.4 mg/kg p.o	Phase I	Pharmacokinetics and efficacy in ameliorating OBD	[54]
0.3 mg/kg every 6 h iv.	Phase I	Safety, pharmacokinetics and efficacy in stimulating GI transit	[56]
0.45 mg/kg iv.	Phase I	Efficacy and safety in preventing OBD	[57]
0.04, 0.08, 0.16, 0.32, 0.64 or 1.25 mg/kg iv.	Phase I	Safety and pharmacokinetics	[58]
0.3 mg/kg iv.	Phase I	Efficacy of methylnaltrexone in ameliorating morphine-induced delay of gastric emptying	[59]
0.3 mg/kg iv.	Phase I	Efficacy in ameliorating urinary retention due to intravenous remifentanil	[25]
0.1 or 0.3 mg/kg sc.	Phase I	Pharmacokinetics and efficacy in ameliorating OBD	[60]
19.2 mg/kg p.o	Phase I	Efficacy of methylnaltrexone in ameliorating pruritus and flushing due to morphine	[66]
0.1 mg/kg daily iv.	Phase II	Efficacy and safety in ameliorating OBD due to chronic methadone	[61]
0.3 or 1.0 mg/kg p.o.	Phase II	Efficacy and safety in ameliorating OBD due to chronic methadone	[62]
1, 5, 12.5 or 20 mg every other day for 3 weeks sc.	Phase II	Efficacy and safety in causing laxation in patients with advanced illness on high-dose opiate medication	[63]
0.3 mg/kg every 6 h for up to 1 week iv.	Phase II	Efficacy and safety in accelerating resolution of POI after open segmental colonic resection	[49]*
0.15 or 0.3 mg/kg sc. as a single dose, followed by *pro re nata* dosing for 4 weeks	Phase III	Efficacy and safety in causing laxation in patients with advanced illness on high-dose opiate medication	[64]*
0.15 mg/kg sc. every other day for 2 weeks, followed by 3-month open-label trial	Phase III	Efficacy and safety in causing laxation in patients with advanced illness on high-dose opiate medication	[65]

Clinical trials that have not yet been fully published.

GI: Gastrointestinal; iv.: Intravenously; OBD: Opioid-induced bowel dysfunction; p.o.: Per os*; POI: Postoperative ileus; sc.: Subcutaneously.*

conventional laxative therapy. The schedule of repeated methylnaltrexone treatment included a double-blind phase for 1 week, followed by an open-label phase for a maximum of 3 weeks. The opioid receptor antagonist was administered every other day at doses comprising 1, 5, 12.5 and 20 mg. The median time to laxation was 1.3 h for all patients receiving a 5 mg or higher dose of methylnaltrexone, and there was no apparent increase in efficacy at doses above 5 mg [63].

Based on this study, two Phase III trials of subcutaneous methylnaltrexone in patients with end-stage diseases suffering from opioid-induced constipation were conducted [64,65]. These multicenter, double-blind, randomized, placebo-controlled studies involved a total of 287 patients in hospice, nursing home or palliative care programs, who had a life expectancy of less than 6 months. Eligible patients were on stable opioid and laxative therapy, but had no laxation for 48 h [64,65]. No rescue laxatives were allowed within 4 h before and after dosing. In the first Phase III study [64], methylnaltrexone (0.15 or 0.30 mg/kg) was administered as a single subcutaneous double-blind dose, 24 h after which the patients were eligible to receive open-label methylnaltrexone *pro re nata* over the next 4 weeks. The primary efficacy end point was laxation within 4 h after a single dose of study drug, a time span within which subcutaneous methylnaltrexone at either dose, unlike placebo, was found to cause laxation in the majority of patients [64].

The other Phase III study was designed to assess the efficacy of subcutaneous methylnaltrexone (0.15 mg/kg) versus placebo administered every other day for 2 weeks in patients

with advanced illness suffering from opioid-induced constipation [65]. Patients were permitted to double the initial volume of the blinded study drug in week 2 if they had fewer than three rescue-free bowel movements in the first week. The 2-week double-blind phase was followed by an open-label extension trial, during which the patients received subcutaneous methylnaltrexone (0.075–0.30 mg/kg) as needed up to every 24 h for up to 3 months [65]. The results showed that within 4 h after receiving the first dose, 48% of the patients treated with methylnaltrexone achieved laxation, relative to 15% of the patients receiving placebo. Similarly, 52% of the patients had a bowel movement within 4 h after two or more of the first four doses of methylnaltrexone, compared with 8% of the placebo-treated patients. This response rate remained consistent throughout the double-blind and open-label extension phase. The median time to laxation was approximately 30 min after administration of methylnaltrexone [65].

POI is another indication in which intravenous methylnaltrexone is being evaluated in Phase II and III trials [49,51]. Patients undergoing open segmental colonic resection were reported to benefit from treatment with methylnaltrexone, as upper and lower bowel function recovered approximately 1 day earlier in patients receiving intravenous methylnaltrexone than in placebo-treated patients, whereas no difference in opioid use or mean pain scores was observed [49]. Subsequently, two Phase III studies were initiated to establish the efficacy and safety of methylnaltrexone in POI [51], one of which ([103]; identifier: NCT00387309) has been completed and its outcome announced in a press release on 13 March 2008 [104]. As the data of this trial show, intravenous methylnaltrexone failed to significantly accelerate postoperative recovery of GI function in patients who underwent segmental colectomy [104]. The results of the other Phase III trial addressing the efficacy of intravenous methylnaltrexone in POI are expected to become available later in 2008.

The beneficial effect of methylnaltrexone is not limited to the GI tract, since urinary retention owing to opioid therapy is also ameliorated by the drug. In a study involving healthy male volunteers receiving intravenous remifentanil, intravenous methylnaltrexone (0.3 mg/kg) was found to partially restore micturition, while opioid-induced miosis remained unaltered [25].

Other adverse actions that opioids exert in some patients include pruritus and flush, which may, in part, be owing to release of histamine from cutaneous mast cells [49]. In human volunteers, it was found that oral methylnaltrexone (19.2 mg/kg) decreased the subjective ratings of 'skin itching' and 'flushing' caused by intravenous morphine [66]. It thus appears as if opioid receptor antagonists with a peripherally restricted site of action could be of benefit in controlling unwanted cutaneous manifestations of opioid therapy. A further effect of opioid analgesics is to suppress the cough reflex, which is an important mechanism to clear and protect the airways. Although this antitussive action is thought to take place in the CNS, preclinical data show that intraperitoneal methylnaltrexone can prevent morphine from inhibiting the cough reflex in guinea pigs, while analgesia remains unabated [67]. Whether methylnaltrexone has a similar effect in humans awaits to be investigated.

Safety & tolerability

At therapeutic doses (0.3–0.45 mg/kg intravenously, and up to 19.2 mg/kg *per os*) methylnaltrexone is well tolerated, an outcome that is also true when methylnaltrexone is repeatedly administered at 0.3 mg/kg intravenously every 6 h [56]. Taking all Phase I studies together, only two types of adverse reactions to methylnaltrexone have been reported (**Table 2**). One of them relates to the vascular system, given that transient orthostatic hypotension can occur at supratherapeutic doses (0.64 mg/kg or higher) and plasma levels of more than 1.4 μg/ml [2,6,49,51]. This reaction may be related to facial flushing and mild light-headedness, symptoms that have occasionally been reported [35]. The other type of adverse effect comprises gut-related reactions such as abdominal cramps, soft stools and diarrhea [2,6,49,51,56,63].

This safety profile was confirmed in Phase II and III trials of patients with advanced illness. In these studies, most adverse effects of intravenous methylnaltrexone affected the GI system, were mild in intensity, did not reduce analgesia or cause opioid withdrawal symptoms, and did not lead to discontinuation of the drug [63–65]. The most common adverse events were transient abdominal pain (in up to 45% of patients), diarrhea, flatulence and nausea.

Economic implications

The opportunity to specifically suppress unwanted effects of opioid analgesics in the periphery has important healthcare implications in the treatment of conditions ranging from

Table 2. Overview of significant adverse effects of methylnaltrexone and its competitor alvimopan, relative to placebo, encountered in clinical trials.

Drug, dose and route of administration	Adverse effects	Ref.
Methylnaltrexone up to 0.3 mg/kg sc., up to 0.45 mg/kg iv., up to 19.2 mg/kg p.o.	No adverse effects of clinical importance in healthy volunteers	[25,53,56,57,60]
Methylnaltrexone 0.64 or 1.25 mg/kg iv. at plasma levels in excess of 1.4 µg/ml	Orthostatic hypotension, facial flushing and light-headedness in healthy volunteers	[58]
Methylnaltrexone 0.3 or 1.0 mg/kg p.o.	No adverse effects of clinical importance in methadone-maintained subjects	[62]
Methylnaltrexone 0.1 mg/kg iv.	Mild-to-moderate abdominal cramping in methadone-maintained subjects	[61]
Methylnaltrexone 0.3 mg/kg iv.	No adverse effects of clinical importance in healthy volunteers; reduction of nausea and vomiting caused by remifentanil	[25]
Methylnaltrexone 0.3 mg/kg every 6 h for up to 1 week iv.	No adverse effects of clinical importance in postoperative patients; reduction of nausea, vomiting and abdominal pain	[49]*
Methylnaltrexone 1, 5, 12.5 or 20 mg every other day for 3 weeks sc.	Gut-related adverse effects of mild intensity: abdominal pain, flatulence, diarrhea and nausea	[63]
Methylnaltrexone 0.15 or 0.3 mg/kg sc. as a single dose, followed by *pro re nata* dosing for 4 weeks	Gut-related adverse effects of mild intensity: abdominal pain, flatulence and diarrhea	[64]*
Methylnaltrexone 0.15 mg/kg sc. every other day for 2 weeks, followed by 3-month open-label trial	Gut-related adverse effects of mild intensity: abdominal pain and flatulence	[65]
Alvimopan 4 or 12 mg p.o.	No significant adverse effects in healthy volunteers	[2,40–42]
Alvimopan 1 mg p.o.	Bowel-related adverse effects (abdominal cramping, nausea, vomiting and diarrhea) in patients receiving chronic opioid therapy	[43]
Alvimopan 1, 6 or 12 mg p.o.	No significant adverse effects in postoperative patients	[2,31,41,45–47]
Alvimopan 6 or 12 mg p.o.	No change (one study) or reduction (two studies) of nausea and vomiting in postoperative patients	[2,46]
Alvimopan 0.5 mg twice daily for 12 months p.o.	Numerical imbalance in ischemic cardiovascular events, neoplasms and fractures in patients receiving alvimopan, relative to placebo	[41,101]*

**Clinical trials that have not yet been fully published.*
iv.: Intravenously; p.o.: Per os*; sc.: Subcutaneously.*

malignant and nonmalignant chronic pain to POI. The immediate benefit for the patient lies in a significant improvement in the quality of life due to the prevention of some of the most disabling adverse effects of opioids. In addition, there are important economic implications that may emerge from the use of methylnaltrexone. The use of this specific adjunct to opioid therapy in patients with chronic malignancy-associated pain may reduce the burden of hospice, nursing home and palliative care programs to provide patient care. If the duration of postoperative hospitalization can be shortened by up to 1 day owing to accelerated recovery of postoperative bowel function, a significant reduction of direct and indirect healthcare costs can be achieved [31,41].

Regulatory affairs

Methylnaltrexone has been developed jointly by Progenics Pharmaceuticals (NY, USA) and Wyeth Pharmaceuticals (NJ, USA) for the management of the unwanted effects of opioid analgesics in the periphery. In 2008, subcutaneous methylnaltrexone was approved by Health Canada and the FDA for the management of opioid-induced constipation in patients with advanced illness who receive opioids for palliative care, but do not appropriately respond to laxative therapy [68,105]. The decision from the FDA came on the same day on which the European Medicines Agency's Committee for Medicinal Products for Human Use issued a positive opinion on the drug for the same indication [106]. In addition, Progenics and Wyeth developed an oral formulation of methylnaltrexone for

the management of opioid-induced constipation in patients with chronic non-malignant pain, and have initiated Phase II trials to test its efficacy and safety in this indication ([103]; identifiers: NCT00547586 and NCT00605644).

Based on promising Phase II results, intravenous methylnaltrexone was granted fast-track status for evaluation of its efficacy and safety in POI by the FDA in 2006 [51]. However, a press release on 13 March 2008 revealed that a Phase III trial of intravenous methylnaltrexone ([103]; identifier: NCT00387309) failed to significantly accelerate recovery from POI caused by segmental colectomy [104]. The outcome of another Phase III trial of methylnaltrexone in POI is due to be released later in 2008, and will be of prime relevance to the further development of the drug as a POI therapy.

Conclusion

Like oral naloxone and alvimopan, subcutaneous and intravenous methylnaltrexone offers the potential to pharmacologically dissociate the peripheral unwanted effects of opioid analgesics from their central action to control pain. By preventing or attenuating opioid-induced constipation, POI, urinary retention and pruritus, this drug can significantly improve opioid therapy. The full advantage of this new treatment concept will be seen if methylnaltrexone proves efficacious and well tolerated not only in the short term, but also in the long term.

Opiates will remain the mainstay in the treatment of moderate to severe pain in the foreseeable future, given that the introduction of analgesic drugs with equal efficacy but a more favorable safety profile is not yet in sight. Thus, any measure that improves the tolerability of opioid analgesics represents a progress in the treatment of pain [2]. The GI tract is one of the major targets of the undesired effects of opiates in the periphery, because the enteric nervous system expresses all major subtypes of opioid receptors. OBD is a serious drawback to the patients' satisfaction with opioid analgesics, and the use of opioids for postoperative pain control prolongs hospitalization because of their potential to prolong POI. While the search for opioid-sparing approaches has, in general, been unsatisfactory, the development of opioid receptor antagonists with restricted access to the CNS has opened up a new avenue to significantly improve opioid therapy. The pharmacological dissociation of OBD and analgesia allows for a more aggressive use of opioid analgesics with better pain relief but fewer side effects [3].

Unlike its direct competitor, oral alvimopan, methylnaltrexone can be administered by the oral, subcutaneous and intravenous route to manage the peripheral adverse effects of opiates. Since oral drug intake may be impossible in seriously ill or postoperative patients, the parenteral route of administration represents an important advantage of methylnaltrexone [51]. This pharmacokinetic versatility of methylnaltrexone combines favorably with its safety profile, whereas the future of alvimopan is overshadowed by its potential long-term toxicity. Although methylnaltrexone's potency at opioid receptors is inferior to that of alvimopan, it is difficult to tell whether this translates to an appreciable difference in clinical efficacy because no comparative studies have thus far been carried out.

Further clinical studies are needed to define the optimal dosage, optimal dosing regimen and optimal efficacy/safety profile of methylnaltrexone in the long term [2]. The available data indicate that, at therapeutic doses, methylnaltrexone has a favorable short-term safety profile, the only adverse reactions of note affecting the GI tract. It has been speculated that part of the undesired action of methylnaltrexone on the bowel reflects a withdrawal reaction, especially in patients who have a history of long-term use of opiates [2]. The therapeutic value of methylnaltrexone can not be fully appreciated before its long-term efficacy and safety have been disclosed. Since methylnaltrexone is likely to be used in multimorbid patients, its interaction with other drugs and the necessity of dose adjustment in patients with renal insufficiency or failure also need to be determined [2,51].

Future perspective

The available data show that methylnaltrexone is able to prevent the peripheral adverse effects of opioid analgesics, while their central analgesic action remains unaltered. Currently approved for the relief of opioid-induced constipation in patients with advanced illness, methylnaltrexone will turn into an important adjunct to opioid therapy of pain if it will prove efficacious and safe in patients with chronic non-malignant pain. Peripherally restricted opioid receptor antagonists may also become useful in other indications. Thus, both methylnaltrexone and alvimopan have been found to stimulate GI transit in healthy volunteers [42,56]. Since the GI opioid system may be overactive under certain pathological conditions, peripherally restricted opioid receptor

Executive summary

Clinical problem

- Opioid analgesics are the mainstay of therapy in many patients with moderate to severe pain, but their therapeutic benefit is severely compromised by adverse effects.
- In the periphery, the unwanted effects of opioids comprise constipation, urinary retention and pruritus.
- The peripheral side effects of opioids can not be managed by nonspecific treatment options (laxatives and prokinetics) in a satisfactory manner.
- Specific management of opioid-induced bowel dysfunction entails selective inhibition of peripheral opioid receptors by opioid receptor antagonists with limited systemic bioavailability and/or a peripherally restricted site of action, such as alvimopan and methylnaltrexone.

Mechanisms of action

- Methylnaltrexone is a μ-opioid receptor-preferring antagonist.

Pharmacokinetic properties

- The quaternary compound methylnaltrexone has limited oral bioavailability and does not enter the brain.
- The major route of elimination is via the kidney.

Clinical efficacy

- Intravenous, subcutaneous and oral methylnaltrexone antagonizes opioid-induced bowel dysfunction, urinary retention and pruritus in healthy volunteers, but leaves the analgesic action of opiates unabated.
- Intravenous and oral methylnaltrexone relieves constipation in methadone-maintained, opioid-dependent volunteers, but does not elicit signs of opioid withdrawal.
- Subcutaneous methylnaltrexone counteracts opiate-induced constipation, but does not impair analgesia, in patients with advanced illness requiring high doses of opiates for pain control.
- Intravenous methylnaltrexone may shorten postoperative ileus and hasten recovery of normal bowel function in patients on opiates following open colectomy.

Safety & tolerability

- Methylnaltrexone is well tolerated, the only effects at therapeutic doses being bowel related (abdominal cramping, flatulence and diarrhea).
- Reports on the long-term safety of methylnaltrexone are not yet available.

Drug interactions

- Information on drug interactions has not yet been released.

Dosage & administration

- Methylnaltrexone has been formulated for intravenous, subcutaneous and oral administration.
- The doses tested in Phase II and III trials are in the range of 0.1–0.3 mg/kg intravenously and subcutaneously, and up to 1 mg/kg perorally.

Regulatory affairs

- In 2008, subcutaneous methylnaltrexone has been approved in Canada, the USA and Europe for the treatment of opioid-induced constipation in patients with advanced illness.
- Phase II studies are underway to evaluate the efficacy and safety of oral methylnaltrexone in the management of opioid-induced bowel dysfunction in patients receiving opioid therapy for chronic non-malignant pain.
- The efficacy of methylnaltrexone in shortening postoperative ileus awaits to be confirmed in additional Phase III studies.

antagonists may become prokinetic drugs in their own right [2,8,69]. In addition, methylnaltrexone can suppress opioid-facilitated HIV infection in human macrophages and inhibit angiogenesis *in vitro*, the latter effect being independent of opioid receptors [51].

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