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EXPERT OPINION

Pharmacologic treatment of opioid-induced constipation

Chong-Zhi Wang & Chun-Su Yuan[†]

[†]*University of Chicago, Pritzker School of Medicine, Department of Anesthesia & Critical Care, Committee on Clinical Pharmacology and Pharmacogenomics, Chicago, IL, USA*

Opioids are potent analgesics for treating moderate to severe pain, but their use is associated with a number of adverse effects, especially opioid-induced constipation (OIC). If the centrally mediated analgesia of opioids could be separated from their peripherally mediated gastrointestinal effects, by a peripherally acting opioid receptor antagonist, opioid-induced bowel dysfunction could be prevented or reversed. There has been considerable interest in peripherally acting opioid antagonists or other compounds to treat OIC. Subcutaneous methylnaltrexone is the first approved therapeutic agent for treatment of OIC, and studies have been conducted using the oral formulation. This editorial contains a brief overview of other selected compounds to treat OIC. Other potential uses of peripherally acting opioid antagonist in clinical practice are also discussed.

Keywords: alvimopan, analgesia, lubiprostone, methylnaltrexone, naloxegol, opioid-induced constipation, opioids, peripherally acting opioid antagonist

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Opioid medications are used extensively as potent analgesics for treating moderate to severe pain. Although opioids offer excellent pain relief, their use is associated with a number of adverse effects because opioid receptors are widespread in different organs of the body. Opioid-induced constipation (OIC) is the most common adverse effect of opioid pain medications, and it can be severe enough to limit opioid use or dose. Reducing the severity of OIC is of utmost importance for patients who benefit from opioids for analgesia. Since opioids mediate their gastrointestinal and analgesic effects through the same subclasses of receptors, i.e., μ, κ and δ, it has been challenging to dissociate the beneficial analgesic effects of opioids from their untoward gastrointestinal effects. One effective approach for dissociation of opioid analgesia from OIC is to separate its central from peripheral activity with a peripherally acting opioid receptor antagonist that does not cross the blood–brain barrier to interfere with analgesia [1].

Methylnaltrexone is a peripherally restricted, μ-opioid receptor-selective antagonist [1]. As a quaternary amine, this compound has a positive charge when in solution and great polarity and low lipid solubility, which restricts its ability to cross the blood–brain barrier. An early study showed that parenteral methylnaltrexone significantly reduced OIC in subjects who took methadone regularly [2]. The subcutaneous formulation of methylnaltrexone is the first approved therapeutic agent for the treatment of OIC in patients with advanced illness when response to laxatives has been insufficient [3]. Compared to the currently approved subcutaneous injection, however, oral administration is a more convenient and safer method for drug delivery [4].

In a Phase III trial, an oral formulation of methylnaltrexone relieved OIC in patients who took opioids for non-cancer pain. In the first 4 weeks of the study, significantly more patients on higher (450 mg), daily doses of the drug had rescue-free bowel movements within 4 h of taking it compared with those who

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received placebo. These effects were maintained throughout an additional 8 weeks during which patients took the drug only as needed [5]. However, compared with a 12 mg subcutaneous dose, a 300 – 450 mg oral methylnaltrexone dose seems high. This dose difference may be attributed to low bioavailability or partial local, luminal activities. The search for effective oral methylnaltrexone formulations has been active [6].

Several other novel peripherally acting opioid receptor antagonists are in development. Naloxegol (NKTR-118) is an investigational drug currently in the most advanced stage for treatment of OIC [7]. Naloxegol was designed using small-molecule polymer conjugate technology with naloxol, a derivative of the non-selective opioid antagonist, naloxone. The naloxegol program consists of two Phase III, 12-week, randomized, placebo-controlled efficacy studies. The 12-week efficacy studies will compare response rate after placebo or two different oral doses of naloxegol. The two doses (12.5 and 25 mg) are lower than the doses used in a previous Phase II trial during which 50 mg resulted in a 31% rate of diarrhea in study patients [8].

Unlike the analgesic effect of opioids, opioid tolerance does not extend to gastrointestinal motility and transit [9]. In other words, OIC persists despite reduced activity in the CNS after repeated opioid use. Chronic opioid users had increased gut sensitivity to methylnaltrexone [2]. Increased sensitivity and the long-term effects of other peripherally acting opioid antagonists, however, may vary among anti-OIC compounds.

The aim of using peripherally acting opioid antagonists is to reduce the side effects of opioids. Ideally, any new compounds should have minimal side effects and no severe adverse effects in key organs. Alvimopan is another approved peripherally acting opioid antagonist that is given to patients to prevent postoperative ileus after partial large or small bowel resection with primary anastomosis [10]. Alvimopan accelerates the gastrointestinal recovery period as measured by time to first bowel movement or flatus. In a long-term Phase III alvimopan safety study, however, increase which was not statistically significant, but the incidence of serious cardiovascular adverse events was greater in patients receiving alvimopan than in the placebo group [11]. This result appeared to prevent further clinical OIC development of the compound. It is necessary to exclude potential cardiovascular adverse events induced by other peripherally acting opioid antagonists.

Commonly reported side effects of peripherally acting opioid antagonists are abdominal pain or cramping, nausea, flatulence, and diarrhea. A precise dosing regimen would be advantageous in reducing these reactions to this class of compounds. Although methylnaltrexone has been administered to thousands of patients, its potential side effects and those of similar compounds should be evaluated in a larger population over extended periods.

Pharmacologically, opioid receptor antagonists should be most effective in reversing opioid agonist-induced actions, including bowel dysfunction. Yet activation or inhibition of other receptors and pathways also can change baseline and drug-induced bowel response. To a certain extent OIC can be managed by different laxatives over variable periods [12]. A non-opioid antagonist, lubiprostone, is a medication used to manage chronic idiopathic constipation and irritable bowel syndrome (constipation type). The compound acts by specifically activating ClC-2 chloride channels on the apical aspect of gastrointestinal epithelial cells, producing a chloride-rich fluid secretion, which softens the stool, increases motility, and promotes spontaneous bowel movements [13]. In a 12-week Phase III clinical study, a 24-mcg capsule of lubiprostone BID effectively treated OIC and now has received FDA approval for this indication [14]. It would be interesting to see how lubiprostone compares with peripherally acting antagonists in chronic opioid users.

Peripherally acting opioid antagonists may be useful to prevent other opioid-induced medical conditions. For example, opioid-induced delay of gastric emptying was reversed by methylnaltrexone [15]. This effect may be beneficial for patients in intensive care units when opioid-reduced gastric motility may decrease the ability to feed patients. Enteric tube feeding is important for nutrition, and the rate-limiting factor for delivering feeds is often the gastric residual after a feed. Methylnaltrexone has the potential to decrease residuals by enhancing gastric emptying, which facilitates enteral nutrition in patients receiving opioid infusions. Another presumably peripheral opioid side effect is urinary retention postoperatively. Reversing opioid-induced urinary retention by peripherally acting antagonists remains to be tested. In addition, after opioid administration, nausea, vomiting and pruritus have been reported. Not all of these opioid side effects are caused by action on the CNS. Peripheral opioid antagonists, which can be used to distinguish peripheral effects from central ones, may reduce some undesirable subjective effects associated with opioid medications [9].

With important new tools, we may get a clearer picture of the anatomical and pharmacologic targets of opioids in different body systems. Novel peripherally acting opioid antagonists should advance our understanding of the sites and mechanisms of a variety of actions of opioids, which may be therapeutically relevant. Peripherally acting opioid antagonists are part of the physician's therapeutic armamentarium for the pharmacologic treatment of OIC.

Declaration of interest

Methylnaltrexone was originally formulated and subsequently modified by faculty at the University of Chicago. It is currently being developed and marketed by Progenics Pharmaceuticals and Salix Pharmaceuticals, to which the lead author serves as a consultant. The University of Chicago and the author stand to benefit financially from the development of methylnaltrexone.

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Affiliation

Chong-Zhi Wang[1] PhD &
Chun-Su Yuan[†2] MD PhD
[†]Author for correspondence
[1]University of Chicago,
Department of Anesthesia & Critical Care,
Chicago, IL, USA
[2]University of Chicago,
Pritzker School of Medicine,
Department of Anesthesia & Critical Care,
Committee on Clinical Pharmacology and
Pharmacogenomics, 5841 S Maryland Ave,
MC 4028, Chicago, IL 60637, USA
E-mail: cyuan@uchicago.edu