aprotinin and lysine analogues in high-risk cardiac surgery. N Engl J Med 2008;358:2319-31.
9. Hiatt WR. Observational studies of drug safety — aprotinin and the absence of transparency. N Engl J Med 2006;355:2171-3.
10. McEvoy MD, Reeves ST, Reves JG, Spinale FG. Aprotinin in cardiac surgery: a review of conventional and novel mechanisms of action. Anesth Analg 2007;105:949-62.
11. Mannucci PM, Levi M. Prevention and treatment of major blood loss. N Engl J Med 2007;356:2301-11.

Opioid Side Effects — Mechanism-Based Therapy

Charles Berde, M.D., Ph.D., and Samuel Nurko, M.D., M.P.H.

Opioid analgesics generate numerous side effects that complicate their use in postoperative care,[1] in the treatment of sickle cell vaso-occlusive episodes, and in the treatment of pain associated with advanced cancer and other life-shortening illnesses.[2] These side effects include sedation, respiratory depression, impaired cognition, nausea and vomiting, loss of appetite, pruritus, urinary retention, impaired orthostatic tolerance, and (perhaps most commonly of all) ileus and constipation. The therapies that are typically used for opioid side effects are rarely evidence-based and are often ineffective.[2]

In this issue of the *Journal,* Thomas et al.[3] describe the results of a multicenter trial of methylnaltrexone for the treatment of opioid-induced constipation in the setting of palliative or hospice care.[3] Opioids induce bowel dysfunction through several expected effects: blockade of propulsive peristalsis, inhibition of the secretion of intestinal fluids, and an increase in intestinal fluid absorption.[4-6] Opioids decrease the activity of both excitatory and inhibitory neurons in the myenteric plexus. In addition, they increase smooth-muscle tone and inhibit the coordinated peristalsis required for propulsion,[4-6] leading to disordered, nonpropulsive contractile activity, which contributes to nausea and vomiting as well as constipation.[4] Several types of pharmacologic agents have been used to treat opioid-induced constipation, including osmotic or lubricant laxatives, stimulant laxatives (orally and rectally), and prokinetics. The effects of such therapies are nonspecific and generally unpredictable, often generating diarrhea or cramps. Furthermore, many patients do not respond to such therapies, so new, more specific, pathophysiologically based treatments are needed.[7]

Previous studies in animals and humans have indicated that antagonism of μ-opioid receptors in the gastrointestinal tract may reverse opioid-induced gut hypomotility.[8,9] The challenge has been to find compounds that can block peripheral receptors without inhibiting the central analgesic effects of opioids. What strategies might work for opioid-induced side effects such as constipation?

Several different drug-development strategies have attempted to reduce side effects by exploiting anatomic barriers to drug distribution. In one strategy, the drug is modified to diminish its access to the sites of side effects while maintaining its access to the sites of intended action, as in the development of "nonsedating" antihistamines that have diminished entry into the central nervous system. A second approach involves local application of drugs to target tissues, with modifications to reduce systemic uptake, as with the administration of inhaled ipratropium, a quaternized muscarinic cholinergic-receptor antagonist that is used in the treatment of asthma and chronic obstructive pulmonary disease.

The use of methylnaltrexone exemplifies a third approach for reducing side effects in a two-drug agonist–antagonist combination. An agonist drug (or prodrug) readily enters the central nervous system for its desired effect, while the antagonist is excluded by the blood–brain barrier but prevents peripheral side effects, as in the combination of levodopa with carbidopa in the treatment of Parkinson's disease. Agonist–antagonist combinations can also be useful, even without differential uptake into different tissues, if the dose–response curves of the agonist and antagonist are widely separated or if there is a different dose response for antagonizing undesirable drug actions versus those that are desirable. The opioid antagonist naloxone can be used to treat nausea, vomiting, and pruritus[9] at an infusion rate that is less than one fifth that generally required to reverse opioid analgesia, although at such rates naloxone does not reverse constipa-

tion, and at higher infusion rates, it reverses analgesia.

Methylnaltrexone is a μ-opioid–receptor antagonist with a quaternary amine structure that prevents substantial entry into most areas of the brain, brain stem, and spinal cord, thereby preserving central analgesic actions of coadministered opioid agonists. Several small brain regions known as the circumventricular organs lack a blood–brain barrier,[10] including the vomiting center in the area postrema in the floor of the fourth ventricle. Methylnaltrexone prevents nausea and vomiting in part by gaining access to opioid receptors in the area postrema.[11] Alvimopan is another peripherally constrained opioid antagonist that was developed for oral use and has a pattern of tissue distribution differing from that of methylnaltrexone. It achieved promising results in clinical trials for treatment of bowel dysfunction,[12] though development is currently suspended pending safety review by the Food and Drug Administration.

The patients who participated in the multicenter trial by Thomas et al. were adults (median age, 71 years) who were receiving opioids for advanced illnesses and had persistent constipation despite the use of laxatives, according to local clinical practice.[3] The patients were randomly assigned to receive either methylnaltrexone or placebo subcutaneously every second day for 2 weeks, with subsequent eligibility for an open-label 3-month extension of the trial.

Methylnaltrexone was at least three times as effective as placebo in producing laxation within 4 hours after the initial dose, and its effectiveness appeared to be undiminished throughout the 2-week double-blind trial, as well as during the 3-month open-label extension. Methylnaltrexone appeared to be safe in this small group of patients, although a larger number of patients will be needed in future studies to detect uncommon adverse events. No episodes of generalized opioid withdrawal or a form of gut hypermotility known as "gut withdrawal syndrome" were observed, and there was no evidence of antagonism of analgesia.

Although methylnaltrexone was significantly more effective than placebo, it was somewhat disappointing that in both phases of the study, the drug produced rescue-free laxation in only about half the patients. There may be several reasons for this failure rate. First, although all the patients were receiving opioids, the predominant causes of constipation among the patients who did not have a response to the drug could have been the effects of other drugs or disease processes unrelated to actions mediated by opioid receptors. Second, although constipation is commonly regarded as a peripheral side effect of opioids, central actions of opioids contribute as well. For example, opioids can reduce the motility of both the small and large intestines through direct actions in the spinal dorsal horn. Future studies in a larger number of patients may help to delineate predictors of the success or failure of methylnaltrexone in specific subgroups of patients and may guide decisions about increasing or decreasing the dose for various patients.

Practical and ethical constraints pose unique challenges for clinical trials involving patients in hospice or palliative care. Collaboration among 27 palliative care centers was required to generate this study, with 133 patients included in the efficacy analysis. Such patients have diverse and medically complex conditions, and it may be difficult to distinguish adverse events caused by a study drug from those caused by the patient's underlying disease or a variety of other coadministered drugs. Thomas et al. should be commended for performing a useful real-world study to benefit this vulnerable group of patients and potentially other patients who need better approaches to the treatment or prevention of opioid side effects.

Dr. Berde reports receiving consulting fees from Endo and Johnson & Johnson, lecture fees from Pfizer, and grant support from Wex Pharmaceuticals; and Dr. Nurko, receiving consulting fees from AstraZeneca, lecture fees and grant support from TAP, and grant support from Sucampo Pharmaceuticals. No other potential conflict of interest relevant to this article was reported.

From the Department of Anesthesiology, Perioperative and Pain Medicine (C.B.) and the Center for Motility and Functional Gastrointestinal Disorders (S.N.), Department of Medicine, Children's Hospital Boston; and the Departments of Anaesthesia (C.B.) and Pediatrics (C.B., S.N.), Harvard Medical School — all in Boston.

1. Kehlet H. Postoperative opioid sparing to hasten recovery: what are the issues? Anesthesiology 2005;102:1083-5.
2. McNicol E, Horowicz-Mehler N, Fisk RA, et al. Management of opioid side effects in cancer-related and chronic noncancer pain: a systematic review. J Pain 2003;4:231-56.
3. Thomas J, Karver S, Cooney GA, et al. Methylnaltrexone for opioid-induced constipation in advanced illness. N Engl J Med 2008;358:2332-43.
4. Wood JD, Galligan JJ. Function of opioids in the enteric nervous system. Neurogastroenterol Motil 2004;16:Suppl 2:17-28.
5. Galligan JJ, Vanner S. Basic and clinical pharmacology of new motility promoting agents. Neurogastroenterol Motil 2005; 17:643-53.

6. De Schepper HU, Cremonini F, Park MI, Camilleri M. Opioids and the gut: pharmacology and current clinical experience. Neurogastroenterol Motil 2004;16:383-94.
7. Pappagallo M. Incidence, prevalence, and management of opioid bowel dysfunction. Am J Surg 2001;182:Suppl:11S-18S.
8. Becker G, Galandi D, Blum HE. Peripherally acting opioid antagonists in the treatment of opiate-related constipation: a systematic review. J Pain Symptom Manage 2007;34:547-65.
9. Cepeda MS, Alvarez H, Morales O, Carr D. Addition of ultra-low dose naloxone to postoperative morphine PCA: unchanged analgesia and opioid requirement but decreased incidence of opioid side effects. Pain 2004;107:41-6.
10. Saper CB, Breder CD. The neurologic basis of fever. N Engl J Med 1994;330:1880-6.
11. Yuan CS. Methylnaltrexone mechanisms of action and effects on opioid bowel dysfunction and other opioid adverse effects. Ann Pharmacother 2007;41:984-93.
12. Wolff BG, Michelassi F, Gerkin TM, et al. Alvimopan, a novel, peripherally acting mu opioid antagonist: results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial of major abdominal surgery and postoperative ileus. Ann Surg 2004;240:728-35.

The Long and Short of a Constipation-Reducing Medication

Arthur J. Moss, M.D.

In this issue of the *Journal*, Camilleri et al.[1] report on their 12-week randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of prucalopride in the treatment of chronic constipation (ClinicalTrials.gov number, NCT00483886). The authors clearly document the efficacy of prucalopride in improving bowel function and quality of life in the 411 patients who received the drug, as compared with 209 patients who received placebo.

However, there is concern about a potential cardiac risk associated with this constipation-reducing drug. Prucalopride is a prokinetic 5-hydroxytryptamine$_4$ (5-HT$_4$) receptor agonist similar in function to cisapride and tegaserod, two constipation-reducing drugs that were voluntarily removed from the market after warnings from the Food and Drug Administration about life-threatening cardiac side effects.[2,3] Cisapride lengthened the period of ventricular repolarization by reducing the slowly activating potassium repolarization current and contributed to sudden death from cardiac causes secondary to prolongation of the corrected QT (QTc) interval in a small number of patients. Tegaserod use was associated with an increase in ischemic events, including angina and stroke, before it was removed from the market in 2007. Will prucalopride, because of its functional overlap with cisapride and tegaserod, be associated with similar adverse cardiac effects?

In view of the known effects of cisapride on the QTc interval, Camilleri et al. provide two references regarding the electrophysiological effects of prucalopride on ion-channel currents in cellular-expression studies.[4,5] The studies indicate that prucalopride has a lower affinity for the human ether-a-go-go–related protein (hERG) channel than does cisapride but that it does inhibit the hERG-channel current in a concentration-dependent manner. Prucalopride significantly slowed channel deactivation and recovery from inactivation,[5] so there are some electrophysiological concerns.

In their study of 620 patients, Camilleri et al. provide important data about the effects of prucalopride on heart rate and the QT interval corrected with the use of Fridericia's formula. Electrocardiograms (ECGs) were obtained at the screening visit and at weeks 4 and 12 during the 12-week treatment period, in which patients received 2 mg or 4 mg of prucalopride or placebo, once daily. The mean QTc values in the two prucalopride groups were similar to that for the placebo group, without any major outliers, so the drug appeared to have no adverse ventricular repolarization effects in this phase 3 trial.

The absence of QTc prolongation reported by Camilleri et al. does not establish the safety of the drug, especially since only a limited number of patients were exposed to the drug for the entire 12-week period. Unfortunately, information about when the ECGs were recorded relative to the prucalopride dosing was not provided, nor was the drug concentration at the time of the ECG recording. In this regard, it would be important to know how prucalopride is metabolized. If it is metabolized by the hepatic cytochrome P-450–3A4 oxidase system, as is the case with cisapride, common medications that inhibit this enzyme system would augment the blood level of prucalopride and could contribute to con-