Editorials

An Opioid Antagonist for Postoperative Ileus

POSTOPERATIVE ileus, a temporary impairment of gastrointestinal motility, occurs universally after major abdominal surgery. This condition exacerbates nausea and vomiting, delays oral feeding, increases postoperative pain, and prolongs hospitalization. Nearly 100 years ago, Cannon and Murphy[1] demonstrated in dogs that opening the peritoneal cavity and manipulating the intestines resulted in a "striking" inhibition of contractile activity in the gastrointestinal tract.

In people, typical postoperative ileus is generally followed by the restoration of motility in the stomach and small bowel within 24 hours; colonic function is recovered over a period of 48 to 72 hours.[2,3] Gastrointestinal transit is modulated by a variety of neural and humoral factors; stimulation of the parasympathetic nervous system increases motility, although tonic sympathetic control, which inhibits motility, normally predominates. Pharmacologic approaches to the treatment of ileus — such as the use of adrenergic blockade, cholinergic stimulation, various prokinetic agents, and prostaglandins — have had limited success. Treatment for ileus is supportive and has changed little since Wangensteen reported in 1932 that nasogastric suction could delay or replace surgical management of bowel obstruction, thereby reducing mortality.[4] Gastric decompression, together with intravenous hydration and electrolyte replacement, remains the standard therapy for ileus.

Although morphine and other opioid drugs are known to intensify ileus, they are extremely effective analgesic agents and are therefore widely used for pain control after abdominal surgery. Opioid medications emulate the actions of endogenous opioid peptides. The drugs exert their effects through the activation of membrane-bound receptors that are widely distributed in the central nervous system. Receptor-binding studies, molecular cloning techniques, and advances in recombinant DNA methods have led to the identification of three main classes of opioid receptors — μ, δ, and κ — as well as subtypes within each class.[5,6] The activation of μ receptors in the brain (μ_1) and spinal cord (μ_2) is responsible for the analgesia induced by morphine and most other opioids used clinically. In addition, μ_2 receptors are present in the brain stem as well as in the gastrointestinal tract; activation of μ_2 receptors results in respiratory depression and reduced gastrointestinal motility.[5] Thousands of synthetic compounds have been developed in efforts to dissociate the desired and adverse effects of opioids by increasing the selectivity of opioid-receptor agonists or antagonists.[6]

Standardized protocols for clinical care — sometimes called "critical pathways" — have recently become popular in efforts to decrease the duration of hospital stays while reducing variation in care and improving its quality. For patients undergoing abdominal surgery, such standardized protocols frequently stress the early removal of the nasogastric tube, early postoperative feeding and ambulation, and minimal use of opioid analgesics.[7-9] Alternative methods of controlling postoperative pain include the administration of nonsteroidal antiinflammatory drugs and epidural infusion of a local anesthetic or a mixture of local anesthetic and opioid. Intraoperative thoracic epidural anesthesia with postoperative epidural analgesia has been shown to have particularly beneficial effects on both pain and the recovery of bowel function after major abdominal surgery.[10,11] Thoracic epidural analgesia not only blocks pain transmission through afferent nerve fibers, thus reducing the need for postoperative opioids, but also inhibits sympathetic efferent nerves in the thoracolumbar region, thereby increasing gastrointestinal blood flow. Furthermore, during thoracic epidural blockade, efferent parasympathetic tone in the sacral region remains unopposed, promoting gastrointestinal motility.

In this issue of the *Journal,* Taguchi et al.[12] report on the selective postoperative inhibition of gastrointestinal opioid receptors. This is a novel approach to the reduction of ileus after major abdominal surgery. Taguchi et al. studied the effects of ADL 8-2698, a potent investigational antagonist of μ-opioid receptors. The drug is administered orally, but oral absorption is limited, and it does not readily cross the blood–brain barrier. Patients who were undergoing a partial colectomy or a total abdominal hysterectomy received one capsule of 1 mg or 6 mg of ADL 8-2698 or an identical-appearing capsule of placebo two hours before surgery and then twice daily until the first bowel movement or discharge from the hospital. Postoperative pain was treated with intravenous, patient-controlled analgesia with conventional μ-receptor agonists (morphine or meperidine).

The patients who received the higher dose of ADL 8-2698 had a faster recovery of gastrointestinal function than those who received placebo, as measured by the time to the first passage of flatus, to the first bowel movement, and to readiness for hospital discharge. The median time to actual discharge was about one day shorter in the group that received the 6-mg dose of ADL 8-2698 than in the group that received placebo. Visual-analogue scores for itching and abdominal cramping were similar in the three groups. It is important to note that analgesia was not inhibited: patients who received ADL 8-2698 at either dose had neither greater use of opioids nor higher maximal pain scores than did those who received placebo.

Taguchi et al. also observed substantial reductions in postoperative nausea and vomiting among patients

who received the 6-mg dose of ADL 8-2698. Postoperative nausea and vomiting are caused by many factors and are highly distressing to patients. Neither alterations in anesthetic technique nor currently available antiemetic drugs consistently prevent these symptoms. The administration of opioids is strongly associated with postoperative nausea and vomiting, possibly through stimulation of opioid receptors in the chemoreceptor trigger zone in the area postrema of the medulla. This area of the brain stem is not protected by the blood–brain barrier; thus, an antagonist of peripheral opioid receptors such as ADL 8-2698 could block opioid receptors in the chemoreceptor trigger zone. Inhibition of input from the chemoreceptor trigger zone to the center that controls vomiting in the medulla would decrease postoperative nausea and vomiting. Future studies should be conducted to determine whether the administration of ADL 8-2698 or other opioid antagonists helps prevent or treat nausea and vomiting after other types of surgery.

Several limitations of the study by Taguchi et al. should be considered. The majority of patients in the study — 63 of 78 — underwent total abdominal hysterectomy. Postoperative ileus tends to be less prolonged after hysterectomy than after many other intraabdominal procedures; the average length of stay after typical abdominal hysterectomy (diagnosis-related-group [DRG] code 355) is 2.78 days.[13] The effect of ADL 8-2698 on postoperative gastrointestinal function in patients undergoing other intraabdominal surgical procedures is uncertain. As noted by the authors, the patients in this study did not receive epidural analgesia. It remains to be determined whether the combination of ADL 8-2698 and epidural analgesia is safe or beneficial. The potential role of ADL 8-2698 in patients with chronic pain, in whom opioid-related constipation can be a major problem, should also be evaluated.

Will ADL 8-2698 or other opioid antagonists be advantageous for patients undergoing abdominal surgery? Taguchi et al. have demonstrated the feasibility of selectively antagonizing an undesirable peripheral effect of opioids (the inhibition of gastrointestinal motility) while preserving the desired central effect (the relief of pain). A one-day decrease in the length of stay after abdominal surgery would have substantial clinical and financial benefits. The administration of a pill is a simple, appealing approach to the treatment of postoperative ileus, free of the technical demands of thoracic epidural infusions.

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BONE LOSS ACCOMPANYING MEDICAL THERAPIES

IN this issue of the *Journal,* two groups of investigators report that the treatment of a primary medical condition resulted in accelerated bone loss.[1,2] In one study, by Smith et al.,[1] men with prostate cancer who were treated with leuprolide had rapid bone loss, which was prevented in a similar group of men by the addition of pamidronate therapy. In the other study, by Israel et al.,[2] premenopausal women taking inhaled glucocorticoids for the treatment of asthma lost more bone mass than women who were not taking inhaled glucocorticoids. What mechanisms do these two agents of bone loss share?

Decreased production of gonadal hormones definitely contributed to bone loss in the men studied by Smith et al. and may also have contributed to that in the women studied by Israel et al. Gonadal hormones prevent bone loss in adults. Estrogen is an important determinant of bone mass in women, and both androgen and estrogen determine bone mass in men. Stone et al.[3] found that bone loss from the total hip was eight times as great in elderly women with estradiol levels below 5 pg per milliliter as in women with levels of 10 pg per milliliter or higher. When given on a long-term basis, leuprolide, a gonadotropin-releasing hormone agonist, inhibits gonadotropin secretion and ovarian and testicular steroidogenesis. In men, leuprolide dramatically lowers the levels of estradiol as well