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SELECTIVE POSTOPERATIVE INHIBITION OF GASTROINTESTINAL OPIOID RECEPTORS

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ABSTRACT

Background Postoperative recovery of gastrointestinal function and resumption of oral intake are critical determinants of the length of hospital stay. Although opioids are effective treatments for postoperative pain, they contribute to the delayed recovery of gastrointestinal function.

Methods We studied the effects of ADL 8-2698, an investigational opioid antagonist with limited oral absorption that does not readily cross the blood–brain barrier, on postoperative gastrointestinal function and the length of hospitalization. We randomly assigned 79 patients — including 1 whose surgery was canceled — to receive one capsule containing 1 mg or 6 mg of ADL 8-2698 or an identical-appearing placebo capsule two hours before major abdominal surgery and then twice daily until the first bowel movement or until discharge from the hospital. Data were analyzed for 26 patients in each of the three groups; all received opioids for postoperative pain relief. Observers who were unaware of the group assignments evaluated the outcomes.

Results Fifteen patients underwent partial colectomy and 63 underwent total abdominal hysterectomy. Patients given 6 mg of ADL 8-2698 had significantly faster recovery of gastrointestinal function than those given placebo. The median time to the first passage of flatus decreased from 70 to 49 hours ($P=0.03$), the median time to the first bowel movement decreased from 111 to 70 hours ($P=0.01$), and the median time until patients were ready for discharge decreased from 91 to 68 hours ($P=0.03$). Effects in the group that received 1 mg of ADL 8-2698 were less pronounced.

Conclusions Selective inhibition of gastrointestinal opioid receptors by an antagonist with limited oral absorption that does not readily cross the blood–brain barrier speeds recovery of bowel function and shortens the duration of hospitalization. (N Engl J Med 2001;345:935-40.)

ILEUS, a transient impairment of bowel motility, is a common postoperative complication that develops in virtually every patient who undergoes major abdominal surgery.[1] Ileus causes abdominal discomfort, nausea, and vomiting. More important, delayed return of gastrointestinal function and resumption of oral intake are major causes of prolonged hospitalization.[2]

The pathophysiology of postoperative ileus is unclear, and there are no specific pharmacologic treatments.[1-4] Major causes of ileus are surgical manipulation of the bowel and stimulation of opioid receptors.[5] Activation of opioid receptors is common after surgery, not only because the stress of surgery provokes the release of endogenous opioids but also because opioids remain the most common treatment for pain in patients undergoing surgery. Morphine and other opioid analgesics inhibit the release of acetylcholine from the mesenteric plexus, thereby increasing colonic muscle tone and reducing propulsive activity in the gastrointestinal tract.[6-8] Consequently, opioids administered for pain relief delay postoperative recovery of normal colonic motility[7] and prolong postoperative ileus.[9]

The gastrointestinal consequences of endogenous and therapeutic opioids can be moderated by the oral administration of antagonists such as naloxone.[10-12] The difficulty with this approach is that a sufficient amount of opioid antagonist can be absorbed through the gastrointestinal tract to inhibit the analgesic effects of systemic opioids or even precipitate an opioid withdrawal syndrome.[11]

The investigational drug ADL 8-2698 (Adolor, Ex-

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ton, Pa.) is a selective opioid antagonist with extremely limited oral absorption.[13] Unlike other opioid antagonists, ADL 8-2698 is potent, has a long duration of action, is effective when given orally, and does not readily cross the blood–brain barrier.[13] Clinical studies in human volunteers and patients who have undergone dental surgery have shown that ADL 8-2698 reverses opioid-induced inhibition of gastrointestinal motility without antagonizing the analgesic effects of opioids.[14] We therefore tested the hypothesis that selective inhibition of gastrointestinal opioid receptors by ADL 8-2698 would speed postoperative recovery of gastrointestinal function and shorten hospitalization after partial colectomy or total abdominal hysterectomy.

METHODS

Enrollment

The study was conducted at Washington University in St. Louis. One of the sponsors (Adolor) and the investigators collaborated on the protocol design. Patients were enrolled and data were acquired solely by the investigators. The sponsors and investigators each conducted an independent statistical analysis of the data, with similar results.

Patients were enrolled with the approval of the institutional review board at Washington University, and written informed consent was obtained. All patients were 18 to 78 years of age, were generally healthy or had well-controlled systemic disease, and were scheduled for partial colectomy or total abdominal hysterectomy (simple or radical) with general anesthesia.

Patients were excluded if they had been treated with corticosteroids or immunosuppressive drugs within two weeks before surgery, had been given opioid analgesics within four weeks before surgery, or were likely to receive nonsteroidal antiinflammatory drugs after surgery. Patients were also excluded if they had Crohn's disease, a history of abdominal radiation therapy, or a history of treatment with vinca alkaloids.

Preliminary data indicated that the enrollment of 26 patients per group would provide the study with 95 percent power to identify a significant difference of one day in the time to fitness for discharge between the group given the 6-mg dose and the group given placebo at an alpha level of 0.05 with a two-tailed log-rank test.

Protocol

On the day of surgery, patients were randomly assigned in equal proportions to take one capsule of 1 mg or 6 mg of ADL 8-2698 or an identical-appearing placebo with a sip of water two hours before surgery. Computer-generated randomization was stratified according to the type of surgery (partial colectomy vs. total abdominal hysterectomy) and was performed by the staff of the hospital pharmacy. The same drug or placebo was subsequently given twice daily until the first bowel movement, until discharge from the hospital, or for a maximum of seven days.

All the patients received general anesthesia, but anesthetic and surgical management was not otherwise specified by the protocol. Postoperative pain relief was provided by patient-controlled intravenous morphine sulfate or meperidine hydrochloride. Diet and activity were advanced as tolerated; a liquid diet was introduced as early as the first morning after surgery if bowel sounds were detected.

Collection of Data

Demographic data and the type and duration of surgery were recorded. Patients were seen twice daily by the research team, between 6 a.m. and 8 a.m. and between 4 p.m. and 6 p.m. Patients were questioned at each visit and asked to note the time of the first passage of flatus and the first bowel movement. Oral intake was measured until patients could tolerate regular meals. During each visit, patients rated the severity of their nausea, abdominal cramping, pain, and itching on 100-mm visual-analogue scales. Total daily consumption of opioid analgesics was recorded.

Participants were deemed ready for discharge when they could tolerate sufficient oral nutrition to permit the discontinuation of supplemental intravenous fluid, when gastrointestinal function had returned (defined by the passage of flatus), when oral temperature was normal, and when no major complications were present. We also recorded the actual duration of postoperative hospitalization.

Statistical Analysis

The prospectively defined primary efficacy outcomes were the time to the first passage of flatus, the time to the first bowel movement, and the time until the patient was ready for discharge. Secondary outcomes were the time to the first ingestion of liquids, the time to the first ingestion of solids, the time until actual discharge, and the visual-analogue scores for nausea, abdominal cramping, itching, and pain. All analyses were performed on an intention-to-treat basis.

When patients withdrew from the study, administration of drug or placebo ceased. However, evaluation of the patient continued, and all available data were entered into the analysis. The times to events were calculated as the number of hours since the end of surgery. When patients left the hospital before a specific outcome occurred (i.e., tolerance of solid food), the time at which discharge was ordered was considered the time of that event. The actual time of discharge was available for all patients.

The median times to events were compared among the three treatment groups with the use of the log-rank test.[15] We also analyzed the time to events using Cox proportional-hazards survival analysis, with adjustment for types of surgery.[15,16] The relative risks and 95 percent confidence intervals for each set of doses were computed from this model, and P values for both the overall test of differences among the treatment groups and pairwise comparisons were computed with the use of the Wald chi-square test. Kaplan–Meier plots were generated by the LIFETEST procedure (SAS Institute, Cary, N.C.) for all times to events.[15] The average maximal visual-analogue scores at any postoperative point for pain, nausea, itching, and abdominal cramps are reported. The maximal scores were analyzed by the Kruskal–Wallis test.[15,17] The Mantel–Haenszel test was used to evaluate nominal outcomes.

Daily consumption of morphine and meperidine was computed for each patient in milligrams of morphine equivalents (7.5 mg of meperidine equals 1.0 mg of morphine). Only patients who actually received opioids on each day were included in this analysis. Values were compared among the groups with use of the Kruskal–Wallis test.[15,17] All reported P values are two-tailed; a P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Data were collected between January 4, 2000, and July 22, 2000. A total of 185 patients were screened for possible inclusion. A total of 79 patients met the inclusion criteria, provided consent, and underwent randomization, including 1 patient assigned to the 1-mg dose of ADL 8-2698 whose surgery was canceled; there were thus 78 patients whose data could be analyzed (26 patients per group).

Fifteen patients underwent partial colectomy, and 63 patients underwent total abdominal hysterectomies. Four patients who were assigned to placebo and eight patients who were assigned to 1 mg of ADL 8-2698 withdrew from the study; none of the patients assigned to 6 mg of ADL 8-2698 withdrew. The average (±SD) number of doses administered was 6.0±2.5 for those assigned to placebo, 5.2±2.6 for those assigned to the

1-mg dose, and 5.3±1.5 for those assigned to the 6-mg dose. Demographic and surgical characteristics were similar in the three groups (Table 1).

The time to recovery of gastrointestinal function was significantly shorter in the patients given the 6-mg dose of ADL 8-2698 than in those given placebo (Fig. 1). The median time to the first passage of flatus decreased from 70 to 49 hours (P=0.03), the time to the first bowel movement decreased from 111 to 70 hours (P=0.01), and the time until patients were ready for discharge decreased from 91 to 68 hours (P=0.03) (Table 2).

Consumption of liquids and solids as well as actual discharge from the hospital occurred significantly earlier in patients given the 6-mg dose of ADL 8-2698 than in those given placebo (Table 2). Dose dependence was evident, with 6 mg being significantly more effective than 1 mg. The 6-mg dose of ADL 8-2698 improved all major outcomes, with and without correction for the type of surgery (Tables 2 and 3).

Visual-analogue scores for pain, itching, and abdominal cramping were similar in the three groups, and the use of opioids decreased as a function of postoperative time and was similar in the three groups. In contrast, there was significantly less nausea in patients given the 6-mg dose of ADL 8-2698 than in those given the 1-mg dose or placebo (Table 2). A beneficial effect of ADL 8-2698 on nausea is supported by our observation that only 27 percent of the patients given the 6-mg dose of ADL 8-2698 reported visual-analogue scores for nausea exceeding 20, as compared with 63 percent in the group given placebo and 67 percent in the 1-mg group (P=0.003). Furthermore, the frequency of vomiting was 23 percent and 26 percent in the placebo group and the 1-mg group, respectively, and 0 percent in the 6-mg group (P=0.03).

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	PLACEBO (N=26)	1 mg OF ADL 8-2698 (N=26)	6 mg OF ADL 8-2698 (N=26)
Age (yr)	54±12	56±9	49±13
Weight (kg)	76±15	80±20	83±23
Female sex (no.)	23	23	24
Height (cm)	168±8	165±8	165±10
Type of surgery (no.)			
Colectomy	6	5	4
Simple hysterectomy	10	14	13
Radical hysterectomy	10	7	9
Intraoperative fentanyl (μg)	256±173	210±85	252±135
Intraoperative morphine (mg)	18.6±13.4	14.8±10.8	17.4±11.7
Duration of surgery (hr)	2.4±0.7	2.1±0.8	2.2±0.8

*Plus–minus values are means ±SD. None of the differences were statistically significant.

DISCUSSION

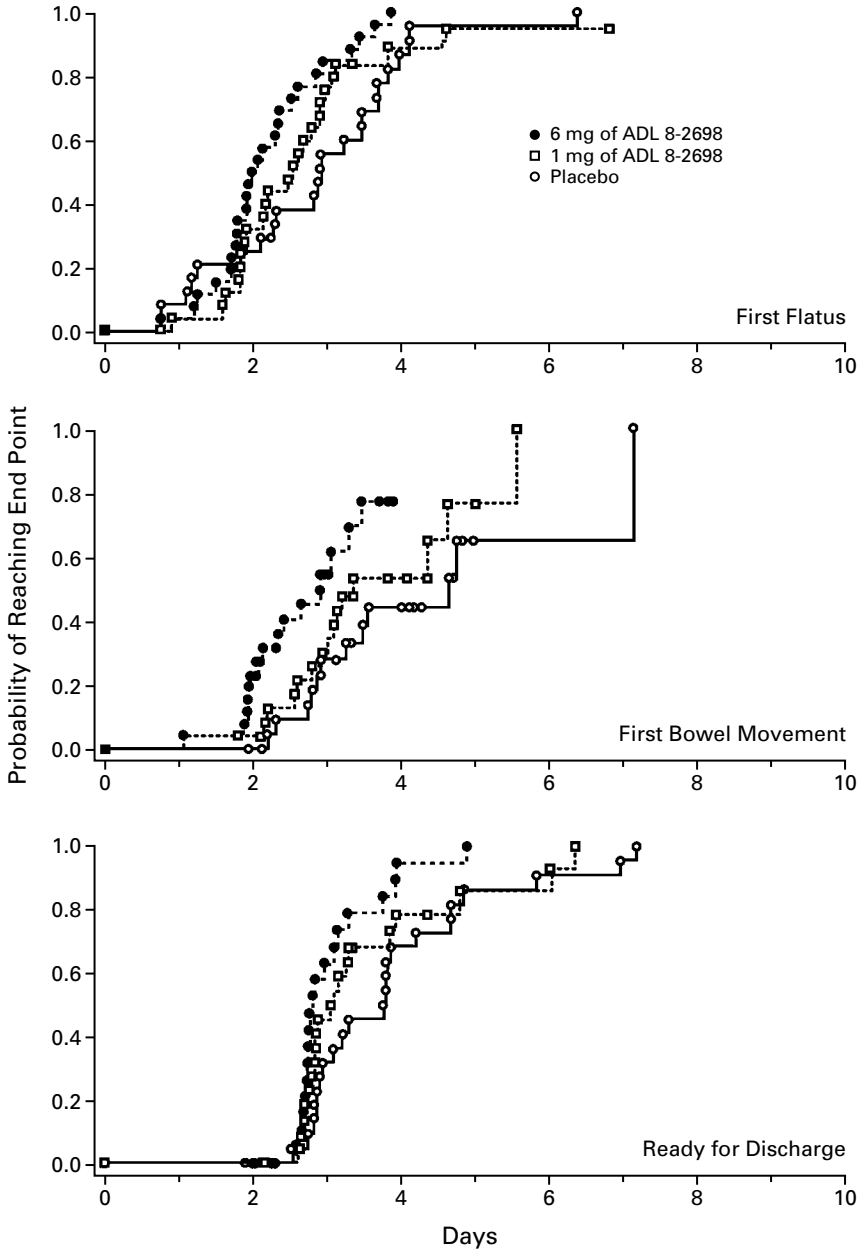
Ileus contributes to postoperative discomfort and increases morbidity. Because patients are unable to eat, self-sufficiency is delayed, the hospital stay is prolonged, and the cost of medical care increases.[2]

Ileus is often considered a physiologic response to abdominal surgery. A variety of management techniques have been used in attempts to prevent it or reduce its duration.[1,3] For example, prokinetic agents such as metoclopramide are commonly given to patients after surgery. However, clinical trials suggest that prokinetic agents play little if any part in reducing the duration of postoperative ileus.[4] Treatment of postoperative ileus thus remains largely supportive, consisting of the administration of intravenous fluid and nasogastric suction.

Activation of opioid receptors prolongs postoperative ileus. This is an important mechanism, because opioids are the most common treatment for intraoperative and postoperative pain. Although effective as analgesics, opioids increase gastrointestinal tone and intraluminal pressure while simultaneously inhibiting organized propulsive motility.[6,7,18] Opioid analgesics significantly delay recovery from postoperative ileus[1,19]; their detrimental effects occur with both epidural and parenteral administration.[20]

Central and local gastrointestinal opioid receptors contribute to the prolongation of postoperative ileus, but it is likely that gastrointestinal receptors have a more dominant role.[6-8,21] All opioid antagonists currently approved for prescription use in the United States readily cross the blood–brain barrier. Systemic opioid antagonists have been used to treat the effects of opioids on gastrointestinal function. For example, intravenous methylnaltrexone — an investigational agent that is not approved for prescription use — reverses opioid-induced constipation in patients with cancer who are receiving long-term therapy with opioids[22] and reverses delays in oral–cecal transit time without affecting analgesia in volunteers given morphine.[23] After oral administration, methylnaltrexone is systemically absorbed but does not cross the blood–brain barrier. However, it has not been evaluated in patients after surgery. Infusions of naloxone and nalmefene have been evaluated in similar studies.[24,25] Although small doses of these drugs can reduce the incidence of postoperative nausea,[24,25] larger doses antagonize analgesia.

ADL 8-2698 differs from other opioid-receptor antagonists in that it is potent, orally active, and poorly absorbed after oral administration. Once absorbed, the drug has a limited ability to cross the blood–brain barrier. Large doses of ADL 8-2698 thus have the potential to antagonize gastrointestinal opioid receptors nearly completely without inhibiting the beneficial analgesic action of systemic opioids.[14] Our results suggest that gastrointestinal opioid receptors play an important part in recovery from postoperative ileus, since recov-



No. at Risk						
6 mg of ADL 8-2698	26	26	19	2	0	0
1 mg of ADL 8-2698	26	26	24	9	4	1
Placebo	26	26	24	11	4	1

Figure 1. Kaplan–Meier Estimates of the Primary Efficacy Outcomes of Time to the First Passage of Flatus, Time to the First Bowel Movement, and Time until the Patient Was Ready for Discharge.

ery of gastrointestinal function occurred earlier in patients assigned to the higher dose of ADL 8-2698 than in patients assigned to the lower dose or placebo. Patients given the higher dose also had less nausea and vomiting and tolerated feedings earlier. More important, patients given the higher dose of ADL 8-2698 were discharged from the hospital a day earlier.

The analgesic efficacy of systemic opioids was not inhibited, as evidenced by similar pain scores and daily consumption of opioids in the three groups. Furthermore, there were no apparent adverse events related to the administration of ADL 8-2698. These observations are consistent with data showing that ADL 8-2698 is minimally absorbed after being given orally

TABLE 2. POSTOPERATIVE CONSUMPTION OF MORPHINE, ADVERSE EFFECTS, AND MEDIAN TIMES TO OUTCOMES.*

VARIABLE	PLACEBO (N=26)	1 mg OF ADL 8-2698 (N=26)	6 mg OF ADL 8-2698 (N=26)	P VALUE
		mean ±SD		
Cumulative morphine sulfate (mg)	71±58	70±61	71±52	0.91
Maximal pain (mm)†	54±25	62±24	53±21	0.30
Maximal nausea (mm)†	38±28	38±33	18±26	0.02
Maximal itching (mm)†	16±28	25±29	28±36	0.48
Maximal abdominal cramping (mm)†	30±29	38±31	21±24	0.13
		median (interquartile range)		
Time to first passage of flatus (hr)	70 (48–88)	61 (46–72)	49 (43–63)	0.03
Time to first bowel movement (hr)	111 (70–171)	80 (67–111)	70 (50–83)	0.01
Time to first liquids (hr)	38 (26–60)	30 (21–41)	26 (18–40)	0.14
Time to first solids (hr)	92 (69–112)	69 (64–93)	59 (52–68)	<0.001
Time until ready for discharge (hr)	91 (70–112)	74 (67–94)	68 (65–68)	0.03
Time until actual discharge (hr)	100 (79–121)	93 (75–118)	71 (56–89)	<0.001

*P values refer to differences among the three groups. The morphine doses include the morphine-equivalent doses of meperidine hydrochloride (7.5 mg of meperidine equals 1.0 mg of morphine).

†Values were measured on a visual-analogue scale.

TABLE 3. PROPORTIONAL HAZARDS FOR THE PRIMARY AND SECONDARY OUTCOMES FOR EACH TREATMENT GROUP ADJUSTED FOR TYPE OF SURGERY.*

OUTCOME	1 mg OF ADL 8-2698 VS. PLACEBO		6 mg OF ADL 8-2698 VS. PLACEBO		6 mg OF ADL 8-2698 VS. 1 mg OF ADL 8-2698		OVERALL P VALUE
	RISK RATIO (95% CI)	P VALUE	RISK RATIO (95% CI)	P VALUE	RISK RATIO (95% CI)	P VALUE	
Time to passage of first flatus	1.2 (0.6–2.2)	0.59	2.5 (1.4–4.7)	0.004	2.1 (1.2–3.9)	0.02	0.007
Time to first bowel movement	1.2 (0.5–2.6)	0.69	2.9 (1.3–6.6)	0.01	2.5 (1.1–5.3)	0.02	0.02
Time to first liquids	1.5 (0.8–2.6)	0.21	1.9 (1.0–3.4)	0.04	1.3 (0.7–2.3)	0.39	0.11
Time to first solids	1.3 (0.7–2.5)	0.38	3.7 (2.0–7.2)	<0.001	2.8 (1.5–5.3)	0.001	<0.001
Time until ready for discharge	1.2 (0.6–2.2)	0.48	2.4 (1.3–4.7)	0.003	2.0 (1.0–4.9)	0.04	0.008
Time until actual discharge	1.4 (0.8–2.6)	0.24	4.3 (2.2–8.2)	<0.001	3.0 (1.7–5.4)	<0.001	<0.001

*There were 26 patients in each group. CI denotes confidence interval. P values are for the comparison between the specified groups.

to animals (ADL 8-2698 has only a 0.05 percent oral bioavailability in dogs).[13] Other recent clinical studies have shown that oral administration of 4 to 9 mg of ADL 8-2698 to normal volunteers selectively antagonizes morphine-induced inhibition of upper- and lower-bowel motility without antagonizing analgesia.[14,26]

More than 400 subjects have received ADL 8-2698 to date.[14,26] In preclinical toxicity testing, ADL 8-2698 was well tolerated and did not produce toxic effects at oral doses of 100 and 200 mg per kilogram of body weight per day for six months in dogs and rats, respectively.[13]

A limitation of our protocol is that enrollment was restricted to patients given opioids for postoperative pain relief. ADL 8-2698 may be less effective in patients treated with epidurally administered local anesthetics. It is also unknown whether the drug will provide a similar benefit in patients undergoing other types of surgery. Twelve patients withdrew from the study after surgery. However, there was no obvious pattern to the withdrawals (most were in the group given the 1-mg dose of ADL 8-2698). It is unlikely that the number of dropouts markedly altered our results.

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Drs. Carpenter and Seyedsadr are employees of Adolor Corporation and contributed to the study design and statistical analysis; they were not involved in obtaining informed consent from participating patients or in collecting or verifying data. None of the other authors have any financial interest in the study.

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