Use of selective opiate receptor inhibitors to prevent postoperative ileus

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Ileus is a common postoperative complication after major abdominal surgery. Surgical manipulation of the bowel and stimulation of opioid receptor are the main causes of ileus. An investigational drug (ADL 8-2698, Alvinopam) a selective opioid antagonist with a very low oral absorption was recently introduced to clinical medicine. Unlike other opioid antagonist its activity is restricted to GI tract, it is potent, has a long duration of action, is orally effective, does not readily cross the blood-brain barrier even after intravenous administration in animals.

Two randomized controlled clinical studies tested its effects in humans. Liu et al.'s study confirmed peripheral restriction of ADL 8-2698 by its lack of central effect on morphine analgesia and pupil miosis. They also showed that ADL 8-2698 prevents increases in gastrointestinal transit time. Taguchi et al. concluded that high dose (6 mg) of ADL 8-2698 archived fast recovery of gastrointestinal function, without antagonising analgesic efficacy of systemic opioid.

In summary, selective inhibition of gastrointestinal opioid receptor by a peripherally restricted oral antagonist speeds recovery of bowel function, shortens times of hospitalization and preserves the analgesic effects of opioids.

Key words: Ileus, opiate receptor inhibitor - Alvinopam - Review

Ileus is a common postoperative complication that develops in nearly all patients undergoing major abdominal surgery. In addition to abdominal discomfort, nausea, and vomiting; ileus delays return of gastrointestinal function and resumption of oral intake. It therefore frequently prolongs hospitalization. The major pathophysiology of postoperative ileus is unclear. Therefore, no standard regimen is available for treatment.
Major causes of ileus are surgical manipulation of the bowel and stimulation of opioid receptors. Activation of opioid receptors is common in postoperative patients because the stress of surgery provokes release of endogenous opioids, and more importantly opioids remain the most common treatment for surgical pain. Morphine and other opioid analgesics inhibit acetylcholine release from the mesenteric plexus, thereby increasing colonic muscle tone and reducing propulsive activity in the gastrointestinal tract. Consequently, opioids delay recovery of normal postoperative colonic motility and prolong postoperative ileus.

Opioid antagonists such as naloxone can antagonize the gastrointestinal side effects of opioids when given orally. However, the difficulty with this approach is that sufficient drug to be absorbed by the gastrointestinal tract can also antagonize the analgesic effects of systemic opioids and even can precipitate a central opioid withdrawal syndrome.

An investigational drug (ADL 8-2698, Alvinopam), a selective opioid antagonist with extremely limited oral absorption was recently introduced to clinical medicine. Unlike other opioid antagonists, ADL 8-2698 is potent, has a long duration of action, is orally effective, and does not readily cross the blood-brain barrier even after intravenous administration in animals. Two randomized controlled clinical studies in humans have been published. This brief review will cover some important aspects of these articles.

Materials and methods

Liu et al. recently reported their results with ADL 8-2698 in healthy human subjects (age 18-45 yr; ASA I). This was a double blind, placebo-controlled, randomized, crossover study. They tested the hypothesis that ADL 8-2698 shortens the gastrointestinal transit time compared to placebo, and that postoperative pain is well controlled in spite of oral selective opioid antagonist (ADL 8-2698) use. Gastrointestinal transit time was measured by lactulose hydrogen breath test in 14 subjects with oral and intravenous placebo, oral placebo and intravenous morphine (0.05 mg/kg), and oral ADL 8-2698 (4 mg) and intravenous morphine (0.05 mg/kg).

Liu et al. also reported the results of forty-five healthy patients who were undergoing third molar extraction were enrolled in a parallel, randomized, double blind study to examine effects of ADL 8-2698 on morphine analgesia. Patients were randomly assigned, postoperatively, to receive ADL 8-2698 (4 mg) or placebo and intravenous morphine (0.15 mg/kg) or to receive oral and intravenous placebo. Analgesia and pupil constriction were measured.

Taguchi et al. studied 79 patients (ASA I-III; age 18 to 78 yrs) who were scheduled for partial colectomy or total abdominal hysterectomy (simple or radical) with general anesthesia. On the day of surgery, patients were randomly assigned to receive ADL 8-2698 (1 or 6 mg) or placebo orally with a sip of water two hours before surgery. Randomization was stratified by type of surgery (colectomy vs total abdominal hysterectomy) and was performed by the hospital pharmacy. The same drug was subsequently given twice daily until the first bowel movement, discharge from hospital, or for a maximum of seven days. Postoperative pain relief was provided by patient-controlled intravenous morphine sulfate or meperidine hydrochloride. Patients were questioned at each visit and asked to note the time of first flatus and first bowel movement. During each visit, patients rated the severity of their nausea, abdominal cramping, pain, and pruritus on 100-mm-long visual analog scales. Total daily opioid analgesic consumption was recorded. The prospectively defined primary efficacy outcomes were time to first flatus, time to first bowel movement, and time until patients were ready for discharge.

Results

In Liu et al.’s study, morphine prolonged gastrointestinal transit time in volu-
teers from 69 to 103 minutes (p=0.005), this was prevented by ADL 8-2698 (p=0.004). In the patient study, morphine analgesia and pupil constriction were unaffected by ADL 8-2698 and both differed from placebo.

In the Taguchi et al. study, 78 patients (fifteen patients had a colectomy and 63 patients had total abdominal hysterectomies) were enrolled. Visual analog pain scores were similar in the three groups; opioid use decreased as a function of postoperative time and was similar for the three groups. In contrast, there was significantly less nausea and vomiting in patients given 6 mg of ADL 8-2698 than in those given 1 mg or placebo. A beneficial effect of ADL 8-2698 on nausea and vomiting was supported by the observation that only 27% of the patients given 6 mg ADL 8-2698 reported visual analog scores for nausea exceeding 20 mm, compared to 63% in the placebo group and 67% in the 1 mg group (p=0.003). Furthermore, vomiting was reduced from 23% in the placebo and 26% in the 1 mg group to 0% in the 6 mg group (p=0.03).

Patients given 6 mg ADL 8-2698 experienced flatus, bowel movement, and consumption of liquids and solids significantly earlier than those given placebo. ADL 8-2698 patients were also fit for discharge and actually discharged significantly sooner. A dose-dependence was clearly evident, with 6 mg being significantly more effective than 1 mg.

Discussion and conclusions

ADL 8-2698 is a selective opioid antagonist that differs from other opioid antagonists, because its activity is restricted to the GI tract. It has very limited systemic absorption after oral administration, has limited ability to cross the blood-brain barrier, and does not possess inherent prokinetic effects. Liu et al.’s study 13 clinically confirmed peripheral restriction of ADL 8-2698 by its lack of central effect on morphine analgesia and pupil constriction. Peripheral restriction of oral ADL 8-2698 to the GI tract selectively antagonized the inhibitory effects of morphine on upper GI transit. Liu et al. concluded that ADL 8-2698 prevents morphine-induced increases in gastrointestinal transit time by means of selective peripheral opioid antagonism without affecting central opioid analgesia.

Similarly, Taguchi et al.14 concluded that gastrointestinal opioid receptors play an important role in recovery from postoperative ileus, and patients assigned to the higher dose (6 mg) of ADL 8-2698 recovered gastrointestinal function faster than patients in the low-dose or placebo groups. Analgesic efficacy of systemic opioids was not antagonized, as evidenced by comparable pain scores and daily opioid consumption.

Furthermore, in both of these published studies, there were no apparent adverse events related to administration of ADL 8-2698. These observations are consistent with data showing that ADL 8-2698 is minimally absorbed after being given orally to animals (ADL 8-2698 has only a 0.05% oral bioavailability in dogs).12 In summary, selective inhibition of gastrointestinal opioid receptors by a peripherally restricted oral antagonist speeds recovery of bowel function, shortens duration of hospitalization, and preserves the pain relieving effects of opioids. Using selective inhibitors of gastrointestinal opioid receptors is thus a possible solution to postoperative opioid-related complications. Therefore, they should seriously be considered as part of the perioperative preventive approach in patients who may receive significant amounts of opioids during surgery and postoperatively.

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Riassunto

L’uso degli inibitori selettivi dei recettori oppiacei nella prevenzione dell’ileo postoperatorio

L’ileo postoperatorio è una complicanza comune dopo interventi chirurgia addominale maggiore. Le principali cause di ileo postoperatorio sono la manipolazione dell’intestino e la stimolazione dei recett-
tori oppioidi. Un farmaco sperimentale recentemen-
te introdotto nella pratica clinica (ADL 8-2698, Alvi-
nopam) agisce come antagonista oppioide selettivo e ha un assorbimento intestinale molto basso. A differenza di altri antagonisti oppioidi la sua azione rimane limitata all’apparato GI, è potente, di lunga durata, è efficace se somministrato per via orale, non attraversa la barriera ematoencefalica dopo somministrazione endovenosa in studi su animali.

Gli effetti sull’uomo sono stati valutati con due studi clinici randomizzati.

Lo studio di Liu et al. ha confermato che il farmaco non ha azione periferica dimostrando che non agisce a livello centrale sull’analgesia condotta con morfina e non causa miosi. Inoltre dimostra che previene l’aumento del tempo di transito intestinale.

Taguchi et al. hanno concluso che alte dosi (6 mg) di ADL 8-2698 consentono una rapida ripresa della funzionalità intestinale, senza antagonizzare gli effetti analgesici degli oppioidi sistemici.

Quindi, il blocco selettivo dei recettori oppioidi gastrointestinali da parte di un antagonista assunto per os e senza azione periferica accelera la ripresa della funzionalità intestinale, accorcia i tempi di ospedalizzazione e preservando gli effetti analgesici degli oppioidi.

Parole chiave: Ileo, inibitori dei recettori oppioidi - Alvinopam - Review

References


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