Molecules of the Millennium

Alvimopan: A novel peripheral opioid receptor antagonist

Introduction

Postoperative ileus (POI) is defined as disruption of normal coordinated movements of the gastrointestinal tract (GIT) resulting in failure of intestinal propulsion. It affects almost all patients undergoing abdominal surgery and is exacerbated by the use of opioids before and after surgery. Following surgery, POI delays mobilization and impedes resumption of normal fluid and food intake. As a result there is prolonged hospitalization following surgery, which has a substantial economic impact on the society. The pathophysiology of POI is unclear and there is no specific pharmacologic treatment.

Major causes of ileus are surgical manipulation of bowel and activation of opioid receptors due to stress-induced release of endogenous opioids. Surgical trauma and manipulation of bowel have been shown to stimulate sympathetic reflexes in the gut and induce release of catecholamines and inflammatory mediators including endogenous opioids that inhibit gastrointestinal (GI) motility and emptying. Moreover, opioid analgesics like morphine and its analogs, widely used to treat postoperative pain, inhibit the release of acetylcholine from mesenteric plexus – thereby increasing colonic muscle tone and reducing propulsive activity in the GIT.

Current management for POI includes measures like minimally invasive surgery, decreased use of opioid analgesics, use of laxatives and prokinetics. However, no treatment is approved by food and drug administration (FDA) for POI in the present scenario. The gastrointestinal consequences of endogenous and therapeutic opioids in POI can be moderated by oral administration of opioid antagonists like naloxone. The disadvantage of this approach is that a sufficient amount of opioid antagonist is absorbed through GIT and inhibits the analgesic effects of systemic opioid or precipitate opioid withdrawal syndrome. This can be overcome by alvimopan, a novel peripherally acting μ opioid receptor antagonist, for the management of acute post operative paralytic ileus and opioid-induced bowel dysfunction.

Chemistry

Alvimopan, formerly known as ADL 8 – 2698, has the molecular formula of C₂₃H₂₈N₂O₂·2H₂O and a moderately large molecular weight of 460.6, in the zwitter ion form. Its polarity limits gastrointestinal absorption, and penetration into blood–brain barrier.

Mechanism of action

There are three types of opioid receptors, namely μ, κ and δ, expressed throughout the central nervous system and in the peripheral regions like GIT. Recently a new opioid receptor has been included, namely nociceptin/orphanin FQ receptor. Peripheral opioid receptors regulate gastrointestinal motility by controlling enteroreceptor and myenteric reflexes. Morphine and other opioids are potent analgesics and act through μ receptors in the brain. However, stimulation of μ receptors in the periphery results in unwanted side effects like opioid bowel dysfunction, constipation and increased gastro-esophageal reflex. Similarly, in vivo animal studies have revealed that endogenous opioids released peripherally can modulate GI motor and secretory functions.

Alvimopan is a novel opioid antagonist that does not cross blood–brain barrier and has selectivity only for peripheral μ opioid receptors. It has been found to be 200 times more potent in peripheral opioid receptors compared to centrally located receptors. In animal models, only at higher doses was alvimopan found to antagonize morphine-induced analgesia by crossing blood–brain barrier.

Pharmacokinetics

Currently available information on pharmacokinetic parameters of alvimopan is mainly from animal models. In these models, alvimopan, after oral administration, appears to be concentrated mainly in GIT. In dogs and rabbits it has shown poor oral absorption, with bioavailability of 0.03% and half life of approximately 10 min. Following intravenous (IV) administration, alvimopan causes dose-dependent increase in peak plasma concentration. Whole body radiography studies conducted after intravenous (IV) administration of (¹⁴C) alvimopan in rats demonstrated that the chemical is detected throughout the body but not in brain or spinal cord. The details of metabolism and excretion are not known from the studies conducted in humans so far.

Clinical trials

In a study conducted by Taguchi et al., 6 mg of alvimopan administered orally in 78 patients showed significantly faster recovery of gastrointestinal function compared to placebo. It was found that the time to the first bowel movement after surgery decreased from 111 to 70 h, and shortened the hospital discharge time from 91 to 68 h. Both these improvements were statistically significant.

A multicentric phase III trial was conducted in 40 centers across USA to evaluate safety and efficacy of alvimopan in 449 patients, both males and females, aged 18–80 years. The selected patients were those scheduled to undergo either partial colectomy or total abdominal hysterectomy, or...
scheduled to receive postoperative pain management with intravenous patient controlled opioid analgesia. They were randomized to an oral dose of either alvimopan (6 mg or 12 mg) or placebo, at least 2 h prior to surgery, and then twice daily from postoperative day 1 to hospital discharge or for a maximum of 7 days. In this study, alvimopan 6 mg bd resulted in statistically significant acceleration in recovery of GI function compared to placebo. However, the study did not show dose-related response of the drug, which possibly may be due to adverse-event related discontinuation of the drug.14

Similar to the study by Delaney et al., another phase III trial was conducted in USA in 34 centers to evaluate the safety and efficacy of alvimopan in 510 patients. This study also showed that GI function was significantly accelerated by 15 h in patients receiving alvimopan and by 22 h in patients given 12 mg alvimopan compared to placebo. The time to hospital discharge was 13 and 20 h earlier with alvimopan 6 mg and 12 mg, respectively, compared with a mean time of 146 h for placebo. However, this was not considered clinically meaningful.15

Alvimopan did not antagonize opioid analgesia as determined by visual analog scale in the above-mentioned trials.13-15

Safety profile

Preclinical and clinical studies have shown that alvimopan is safe and well tolerated.13, 17 Acute and subacute toxicity studies in rats and dogs have revealed that ADL 8-2698 has a large therapeutic index. However, none of the studies revealed any important toxicological findings. Till now, no reproductive or developmental safety issues were identified from preliminary in vitro and in vivo studies.9

Adverse effects

From the trials conducted so far, it seems the most frequent treatment-emergent adverse events were nausea, vomiting and abdominal cramps. However, they were less with alvimopan compared to the placebo group.14, 15

Contraindications

Alvimopan is not recommended for use in severe hepatic failure. In patients with mild to moderate hepatic disease, end-stage renal disease or patients on dialysis, there is a potential for raised alvimopan concentration resulting in adverse effects like abdominal cramps and diarrhea. To date there are no data available on safety and effectiveness of alvimopan in pregnant women and children. It is not preferred for complete bowel obstruction. It is contraindicated in patients who have been treated with opioid for more than 8 days or who have stopped opioid use for at least 7 days prior to initiation of treatment. This is because opioid treatment may lead to gut sensitization, and administration of opioid antagonist may lead to gastrointestinal symptoms of opioid withdrawal. Similarly, patients on chronic opioid therapy should not be given alvimopan following abdominal or pelvic surgeries.14-16

Drug interactions

In vitro studies have shown that alvimopan is a substrate for P–glycoprotein (P-gp). However, pharmacokinetics of alvimopan does not appear to be altered by concomitant drugs which are mild to moderate P–gp inhibitors. It does not influence the pharmacokinetics of morphine.16

Current status

In USA, alvimopan has completed phase III clinical trial and a new drug application is under review by FDA. Though oral doses of 6 mg and 12 mg bd were reported to be well tolerated and used in phase III trials, in the new drug application submitted to FDA in June 2004, the requested indication is for 12 mg capsule. Current data suggest that alvimopan should be administered preoperatively before opioid treatment followed by twice daily for a maximum of 7 days. Trials are on in Europe to evaluate its safety and efficacy.

Conclusion

Alvimopan a novel peripherally acting opioid receptor antagonist shows significant advantage over currently available treatment for POI. Preclinical and clinical studies conducted with alvimopan have demonstrated that opioid antagonism in the gut can be achieved without compromising analgesia.8,13 Thus it is useful in reversing unwanted side effects of opioid analgesics, like constipation, while preserving centrally mediated analgesia. If approved by FDA, alvimopan could be a useful tool in enhancing postoperative recovery of GI function, decreasing the duration of hospital stay and reducing the economic burden of the health care system.

References


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