

Commentary

Opioid-induced constipation in intensive care patients: relief in sight?

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Abstract

Constipation is the most common gastrointestinal complication associated with opioid therapy in chronic pain patients, and also frequently occurs in sedated intensive care unit patients. Conventional therapy may not provide sufficient relief from constipation, which can be severe enough to limit opioid use or the dose. In a recent study on terminally ill patients suffering from laxative-resistant opioid-induced constipation, Thomas and colleagues demonstrated subcutaneous methylnaltrexone to rapidly induce defecation. This appealing result might also have favourable prospects for intensive care patients, as their outcome is often codetermined by recovery of bowel functioning.

Opioid-induced bowel dysfunction remains a clinically important problem that is the source of much suffering, and new treatment approaches are anticipated. Thomas and colleagues should therefore be commended for their important contribution to tackle this problem [6]. In their multicentre trial of 133 terminally ill patients suffering from laxative-resistant opioid-induced constipation, they demonstrated subcutaneous methylnaltrexone to rapidly induce defecation within several minutes to hours. Furthermore, this μ -opioid receptor antagonist had no influence on the overall incidence of adverse events, and neither did it affect central analgesia.

Gastrointestinal complications are very common in patients on intensive care units [1]. The highest occurrence of delayed gastric emptying is observed in patients with head injuries, burns, multisystem trauma, and sepsis [2]. The aetiology of bowel dysfunctions, in some cases progressing to a paralytic ileus, is certainly complex, and major contributing factors on the intensive care unit include parenteral nutrition, mechanical ventilation, hypoperfusion, shock, dehydration, secretion of inflammatory mediators as well as endogenous and exogenous opioids [3].

Oral application of methylnaltrexone is more convenient than injections and, as it acts directly in the bowel, is believed to be safer and more efficient [7]; this approach therefore seems to be an appealing alternative to laxatives. Moreover, repeated administration of intravenous methylnaltrexone has been shown to be well tolerated, with no significant adverse events or changes in opioid subjective ratings and with no clinically noteworthy alterations in pharmacokinetics [8].

Opioids are commonly used on the intensive care unit to treat pain or for sedation; their efficacy is accompanied by burdensome side effects, however, the most frequent being nausea, respiratory depression, impaired cognition, urinary retention, and bowel dysfunction [4]. Opioid-induced bowel dysfunction encompasses delayed gastric emptying accompanied by increased gastroesophageal reflux, as well as constipation [4]. Constipation is not only discomforting but can also cause abdominal distension, vomiting, restlessness, gut obstruction and perforation, and may be associated with aspiration or fatal pulmonary embolism [5]. A large survey in 250 intensive care units has shown that constipation occurs in up to 83% of nonsurgical critical care patients, delaying weaning from mechanical ventilation (28%), delaying enteral feeding (48%) and delaying hospital discharge (18%) [5].

Only about 4% of intensive care units currently have guidelines for treating constipation [5]. Various laxative interventions exist at present; however, despite constipation often being overcome, the time of laxation can be unpredictable [9].

Several types of pharmacologic agents are 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 are generally unpredictable, often generating diarrhoea or cramps [9]. Furthermore, most of these drugs cause severe side effects – such as acetylcholine, which induces bradycardia and increases respiratory secretions; cisapride, a 5HT₄ agonist that is no longer clinically available because of cardiac complications; or metoclopramide, which is believed to have little colonic effect [4].

Stimulant laxatives, such as senna and bisacodyl, can induce painful abdominal cramping upon activation, whereas sugar-based osmotics produce gas that can lead to uncomfortable bloating [4]. Systemic opioid antagonists such as naloxone have been shown to reverse bowel dysfunction, but there was often a clinically unacceptable percentage of unpredictable systemic opioid withdrawal and increased pain [10]. Moreover, many patients do not respond to such therapies. New, more specific, pathophysiologically based treatments are therefore needed. Peripheral selective opioid antagonists such as methylnaltrexone or alvimopan, which do not cross the blood-brain barrier, promise to decrease bowel dysfunctions without any effect on central analgesia. Their antagonism of μ -opioid receptors in the gastrointestinal tract seems to reverse opioid-induced gut hypomotility [9].

Whereas alvimopan has been shown to counter opioid-induced delays in the gastrointestinal transit time, a previous study has been suspended due to an apparent increase in cardiovascular events [11]. The promising therapeutic approach of Thomas and colleagues presented in the *New England Journal of Medicine* to avoid opioid-induced constipation showed no increase of adverse events compared with a placebo group [6]. Moreover, there were no differences in mean pain scores at baseline and at each evaluation of patients between the study group and the placebo group.

As patient outcome is often codetermined by recovery of bowel functioning, these μ -opioid receptor antagonists should also be very effective in intensive care treatment. Delayed defecation on the intensive care unit prolongs the hospital stay and the length of mechanical ventilation whilst increasing the need for vasopressors and opioids, increasing organ failure and increasing mortality [12].

Accelerating gastrointestinal recovery during intensive care could increase patient comfort, decrease the average hospital stay, and reduce costs and readmission rates. This hypothesis should initiate future trials investigating pharmacological anticonstipation strategies with μ -opioid receptor antagonists in our intensive care unit patients.

Competing interests

The authors declare that they have no competing interests.

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