Methylnaltrexone Use in a Seventeen-Month-Old Female with Progressive Cancer and Rectal Prolapse

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Abstract

Background: Opioid-induced constipation is commonly seen in pediatrics, especially at the end of life. As patients clinically decline, constipation often leads to increased pain and distress, while its enteral treatment becomes more challenging.

Method: There is little information about the safety and use of methylnaltrexone in children. We present the case of a 17-month-old girl with progressive leukemia who was at the end of her life and whose severe opioid-induced constipation and rectal prolapse was successfully treated with the μ -opioid-receptor antagonist methylnaltrexone. We selected a lower dose based on our lack of experience with methylnaltrexone in this age group and concern for potential complications given her rectal prolapse.

Discussion: Opioid-induced constipation, abdominal distention, and rectal prolapse caused our patient's most distressing symptoms, even in the context of advanced cancer. A single dose of subcutaneous methylnaltrexone (0.12 mg/kg) resolved her constipation and rectal prolapse within one hour. Although evidence is limited, the drug has successfully been used in pediatric patients with no reported side effects to date. We recommend its use earlier in the course of severe opioid-induced constipation in children unable to tolerate an oral laxation regimen. Prospective research is needed to establish the parameters for use of this effective agent in children who cannot tolerate other regimens.

Introduction

OPIOID-INDUCED CONSTIPATION (OIC) is extremely prevalent at the end of life, when opioids are widely prescribed to treat pain.¹ Constipation is reported to cause suffering in 40% to 50% of pediatric oncology patients during end-of-life care.² Most preventative bowel regimens are enteral preparations, which are increasingly difficult for patients to tolerate as they clinically decline. Despite very little enteral intake at the end of life, the absence of bowel movements can cause severe abdominal distention and discomfort. Methylnaltrexone was developed to induce laxation by competing with opioids for binding to peripheral μ -opioid receptors.³ Its selectivity and inability to cross the blood-brain barrier ensure that the central pain-relieving effect of opioids is not compromised. Although this medication has been well studied in adults, there is little information about its safety and use in children.⁴

Here we present the case of a very young child with progressive leukemia, at the end of her life. She experienced rectal prolapse caused by severe OIC, which was treated successfully with subcutaneous methylnaltrexone.

Case Description

The patient was a 17-month-old girl with progressive acute myelogenous leukemia (AML) diagnosed at 4 months of age. She was referred to our institution's palliative care team before undergoing hematopoietic stem cell transplantation. Her leukemia relapsed shortly after the transplant and she was enrolled in hospice. Throughout her transplant course and afterward, she had occasional bouts of constipation with hard stools and straining. She received an oral laxation regimen of twice-daily polyethylene glycol, docusate, and sennosides. As she continued to decline clinically, a nasogastric tube was placed to provide supplemental nutrition, and her enteral laxation regimen was continued. However, the risk of aspiration increased after further clinical deterioration, and the nasogastric tube was removed. During this time the patient's pain became more difficult to control; doses of opioid were increased, and a continuous intravenous hydromorphone infusion was started (at a 0.09 mg/kg/h morphine equivalent during the 24 hours before administration of methylnaltrexone). Without an enteral laxation regimen, the patient began straining with every stool, showed increasing abdominal

distention, and developed rectal prolapse. As treatment options were limited and she experienced increasing discomfort, 1 mg (0.12 mg/kg) of methylnaltrexone was injected subcutaneously. She passed multiple stools within 60 minutes of injection, her rectal prolapse resolved, and her abdominal distention was considerably reduced.

Discussion

OIC can contribute significantly to discomfort and distress at the end of life. While methylnaltrexone is a known and effective treatment option for adults with OIC,⁴ its effectiveness and safety have not been established in pediatric patients despite several case reports describing its safe and effective use. Our case demonstrates not only the clinical efficacy of methylnaltrexone in a child who was unable to tolerate enteral medications, but also the resolution of rectal prolapse associated with OIC. This child's OIC and rectal prolapse had become the main cause of her suffering, and relief quickly followed administration of the drug. To date, methylnaltrexone has reportedly been used successfully in pediatric patients to relieve OIC, urinary retention, and postsurgical ileus. Our report adds the resolution of rectal prolapse to these positive clinical outcomes.

All case reports to date have demonstrated impressive relief within minutes of methylnaltrexone administration, with no adverse effects, withdrawal, or increased pain; in some cases, lower doses of opioids were required after methylnaltrexone administration. The pediatric oncology patient reported by Kissling and colleagues⁵ had not passed stool for 25 days and had a bowel movement within 10 minutes of subcutaneous methylnaltrexone administration. Similarly, our patient passed multiple stools within 1 hour of administration, relieving her symptoms. In another case reported by Garten and colleagues, a newborn infant had postoperative ileus for 8 days, and intestinal dysmotility was resolved within 15 minutes of intravenous methylnaltrexone administration.⁶ These cases demonstrate not only that methylnaltrexone has been successful in pediatric patients but also that its onset of action is extremely rapid.

Dosing is difficult to determine without established pediatric guidelines. The manufacturer's prescribing information does not address pediatric patients but recommends 0.15 mg/kg subcutaneous for adults weighing less than 38 kg, with "usual" repeat doses every other day but not more frequently than every 24 hours.⁷ Thomas and colleagues performed a prospective, randomized clinical trial to validate the dosing of 0.15 mg/kg/dose subcutaneously in adults.⁴ This information was used to select the methylnaltrexone dose in three of the four cases previously reported, in which 0.15 mg/kg was administered subcutaneously or intravenously, with repeat doses separated by at least 24 hours. One patient who was unable to tolerate injections was given methylnaltrexone enterally at a dose of 0.16 mg/kg, on the basis of a previous report on oral methylnaltrexone.⁸ We selected a lower dose of 0.12 mg/kg/dose given subcutaneously based on our lack of experience with methylnaltrexone in this age group and concern for potential complications given her rectal prolapse. We planned to administer a second dose of 0.15 mg/kg subcutaneously after 24 hours if the

patient experienced no relief, and we considered repeating the methylnaltrexone dose every 24 hours if the OIC and rectal prolapse did not resolve. Previous reports have described as many as five sequential subcutaneous or intravenous doses of methylnaltrexone with no adverse effect, and even more repeat doses were reported to have been administered enterally. Additionally, we have used repeated subcutaneous doses every one to five days in patients with refractory OIC with success. However, if methylnaltrexone is used to promote laxation, we recommend an oral laxation regimen be restarted whenever feasible.

In conclusion, methylnaltrexone appears to be a safe and effective medication for pediatric patients with severe OIC. In light of the consistent efficacy and safety reported, the suffering caused by unrelieved OIC, and the frequency with which other options may be exhausted, we suggest that methylnaltrexone be used before OIC becomes so advanced as to cause the patient severe distress. Our patient would likely have benefited from the use of methylnaltrexone before the development of abdominal distention and rectal prolapse. Use of methylnaltrexone may be able to (1) improve the opioid pain management in pediatric patients unable to tolerate an oral laxation regimen by resolving or preventing adverse effects such as urinary and fecal retention, ileus, and rectal prolapse; (2) improve the comfort of children already in distress or at the end of life; and possibly (3) allow the reduction of opioid doses. Therefore, we propose that prospective pediatric clinical studies of this drug are highly warranted.

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Author Disclosure Statement

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References

1. Greco C, Berde C: Pain management for the hospitalized pediatric patient. *Pediatr Clin North Am* 2005;52(4):995–1027.
2. Wolfe J, Grier HE, Klar N et al.: Symptoms and suffering at the end of life in children with cancer. *N Engl J Med* 2000; 342(5):326–333.
3. Moss J, Rosow CE: Development of peripheral opioid antagonists: New insights into opioid effects. *Mayo Clin Proc* 2008;83(10):1116–1130.
4. Thomas J, Karver S, Cooney GA et al.: Methylnaltrexone for opioid-induced constipation in advanced illness. *N Engl J Med* 2008;358(22):2332–2343.
5. Kissling KT, Mohassel LR, Heintz J: Methylnaltrexone for opioid-induced constipation in a pediatric oncology patient. *J Pain Symptom Manage* 2012;44(1):e1–e3.
6. Garten LP, Degenhardt P, Buhner C: Resolution of opioid-induced postoperative ileus in a newborn infant after methylnaltrexone. *J Pediatr Surg* 2011;46(3):e13–e15.
7. Relistor [Package Insert]. Philadelphia, PA: Wyeth Pharmaceuticals Inc., 2010.

8. Yuan CS, Foss JF, Osinski J, et al.: The safety and efficacy of oral methylnaltrexone in preventing morphine-induced delay in oral-cecal transit time. *Clin Pharmacol Ther* 1997;61:467–475.
9. Lee JM, Mooney J: Methylnaltrexone in treatment of opioid-induced constipation in a pediatric patient. *Clin J Pain* 2012; 28(4):338–341.
10. Garten L, Buhrer C: Reversal of morphine-induced urinary retention after methylnaltrexone. *Arch Dis Child Fetal Neonatal Ed* 2012;97(2):F151–F153.

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