JPPT | Single Center Retrospective Study

Clinical Outcomes of Intravenous Methylnaltrexone in Children: A Single-Arm Retrospective Cohort Study

Michael Raschka, PharmD; Kayla Gahr, PharmD; Dave Watson, PhD; and Melisa Lu, PharmD

OBJECTIVES Constipation is a common adverse event of opioid use that is often difficult to treat. Methylnaltrexone is a therapeutic option for opioid-induced constipation (OIC) approved for oral and subcutaneous use in adults. These administration routes are not always feasible in the pediatric population. The primary objective of this research was to quantify the response rate of methylnaltrexone in pediatric patients when it was administered via the intravenous (IV) route.

METHODS This retrospective study evaluated patients ages <18 years who received IV methylnaltrexone between January 1, 2013, and June 30, 2020, for OIC. Efficacy was evaluated through documentation of bowel evacuation within 4 hours of methylnaltrexone administration. Adverse events observed within 24 hours of administration were attributed to methylnaltrexone.

RESULTS Methylnaltrexone was administered to 134 unique patients during the study period. Of these, 46 met exclusion criteria, resulting in 88 patients being included in the study. Patients with an underlying hematology/oncology diagnosis consisted of 77% of the study population, and 23% of patients had an underlying medical/surgical diagnosis. The response rate to IV methylnaltrexone was 25% (CI, 16–34).

CONCLUSIONS The results of this retrospective chart review demonstrate the potential role of IV methylnaltrexone in the pediatric population. Despite the overall lower response rate relative to that reported in adults, IV methylnaltrexone possesses a unique mechanism of action that may serve as an alternative treatment option for patients unable to use the oral and subcutaneous administration routes. There were no significant adverse events seen in the study.

ABBREVIATIONS ADR, adverse drug reaction; IV, intravenous; OIC, opioid-induced constipation

KEYWORDS constipation; intravenous; methylnaltrexone; oncology; opioid-induced constipation; pediatrics

J Pediatr Pharmacol Ther 2024;29(3):292–298

DOI: 10.5863/1551-6776-29.3.292

Introduction

Constipation occurs in 40% to 90% of patients being treated with opioids for chronic pain.[1] Unlike other adverse events of opioids, such as nausea and sedation, patients do not develop tolerance for constipation while receiving opioid treatment.[2] Bowel regimens are typically used for both prophylaxis and treatment of opioid-induced constipation (OIC), with various laxatives being the primary agents. However, some patients may not respond sufficiently to laxatives and may require additional measures to treat their constipation.

Methylnaltrexone is a quaternary derivative of naloxone that acts peripherally as an antagonist at μ-opioid receptors.[3] Because of its high polarity and low lipid solubility, it does not cross the blood-brain barrier and thus does not induce reversal of analgesia from opioids.[2] Currently, methylnaltrexone is approved for subcutaneous and oral administration to treat OIC in adults with advanced illness and/or chronic noncancer pain.[3,4] In the adult population, subcutaneous use had demonstrated response rates ranging between 34% and 62%.[2,5] Although methylnaltrexone is not yet approved for use in pediatrics, published case series have reported successful bowel movements in pediatric patients treated for OIC with methylnaltrexone.[6,7] Unfortunately, administration via the subcutaneous route is challenging in the pediatric population because needles and injections can cause stress, anxiety, and pain in these patients.[8]

Phase 1 and phase 2 studies have evaluated the intravenous (IV) administration of methylnaltrexone in adult patients.[9–12] These studies have found that when administered by the IV route, methylnaltrexone has a low accumulation rate, secondary to high clearance and a low biologic half-life. Additionally, the studies have shown efficacy in antagonizing opioid-induced effects on the gut while not reversing analgesia or inducing opioid withdrawal. In the literature, there are a few case reports of methylnaltrexone being administered to pediatric patients through the IV

route, but more data on its use in a pediatric population are needed.[13,14]

Children's Minnesota has adopted the practice of administering methylnaltrexone via the IV route, despite the lack of published data. Oral methylnaltrexone is not on formulary at Children's Minnesota, resulting in parenteral methylnaltrexone as the sole opioid antagonist for intermittent use in the treatment of OIC. Intravenous administration provides the opportunity to avoid the psychological stress or pain that comes with subcutaneous administration, especially among patients who already have IV access. The primary focus of this study was to quantify the response rate of methylnaltrexone when administered intravenously to pediatric patients. The secondary objective of the study was to determine and quantify the rates of adverse events associated with IV administration of methylnaltrexone in this patient population.

Methods

Study Design. Eligible patients were identified through the hospital's data warehouse query, using the study period of January 1, 2013, through June 30, 2020. The preliminary patient list provided by the hospital's data warehouse included all patients in the provided time frame that received at least 1 dose of methylnaltrexone. Manual chart review within the electronic medical record was then performed to identify patients that met the inclusion criteria: hospitalized patients who were administered methylnaltrexone by the IV route, were younger than 18 years at the time of methylnaltrexone administration, were being treated with scheduled opioid therapy, were receiving at least 1 bowel regimen agent scheduled at least once daily, and had a minimum of 24 hours of chart notes documented and available following the time of methylnaltrexone administration. For patients who received more than 1 dose of methylnaltrexone, only the results of the initial dose were included in the study, and additional doses were excluded. Patients were also excluded if they received an additional bowel regimen agent within 30 minutes of methylnaltrexone administration, or if they were receiving prokinetic agents, including azithromycin, erythromycin, or metoclopramide.

Data collected included patient demographics (i.e., age, sex, and ethnicity), along with primary diagnosis, body weight, height, body surface area, serum creatinine, liver function tests, and stool output. Use of concomitant medications known to treat constipation within the preceding 24 hours of methylnaltrexone administration were collected through manual chart review. Concomitant administration of continuous infusion naloxone for the mitigation of opioid adverse effects was also noted, as was the administration of vinca alkaloids (vinblastine, vincristine, and vinorelbine) within 30 days prior to the administration of methylnaltrexone. Renal function was evaluated using the modified Schwartz equation for the calculation of creatinine clearance to assess the dosing appropriateness of methylnaltrexone in patients with renal impairment, defined per the package insert as an estimated creatinine clearance of less than 60 mL/min.[4,15,16]

During chart review, the authors confirmed that all doses of IV methylnaltrexone followed the recommended dosing of 0.15 mg/kg (maximum, 12 mg). Additionally, patients with renal dysfunction, defined as an estimated creatinine clearance of less than 60 mL/min, were appropriately dose-adjusted per package insert guidelines.[4] The institutional standard for preparing IV methylnaltrexone consists of drawing up manufacturer-supplied solution, without any additional dilution prior to administration. Intravenous doses were given as a slow push during 3 to 5 minutes with a normal saline flush following the administration of methylnaltrexone.

Response rate was defined as a stool evacuation within 4 hours of methylnaltrexone administration. Stool smears or increased bowel sounds did not meet the criteria of a stool evacuation and were not counted as a response to treatment. Confirmation of response rate was determined using a combination of documented stool output and statements within nursing and provider notes.

Adverse effects that occurred within 24 hours of methylnaltrexone administration were identified and collected from provider and nursing chart notes. Rates of vomiting were obtained from both chart notes and charted emesis events within the electronic medical record. Because of the multiple variables present for each patient that could lead to adverse effects, Naranjo scores, a commonly used scale based on a 10-question assessment, were assigned by the research team to each adverse effect identified.[17] The resulting score categorizes the association between a medication and reported adverse drug reactions (ADRs) as definite, probable, possible, or doubtful.

Statistical Analysis. Summaries of patient characteristics are reported as means for numeric data and frequencies and percentages for categoric data. The response rate is reported as a percentage with a 95% CI, and the χ^2 test was used to assess associations with certain factors, namely, diagnosis type, concurrent naloxone use, and vinca alkaloid use (among oncology patients).

Results

Study Population. A total of 134 patients were identified to have received at least 1 dose of methylnaltrexone during the study period. Of these, 46 were excluded, resulting in 88 patients being included in the cohort (Figure).

Of the 88 patients included, 68 (77%) had an underlying oncology diagnosis (Table 1). Those without an underlying oncology diagnosis had a variety of medical

Figure. Flow diagram for study cohort inclusion and exclusion.

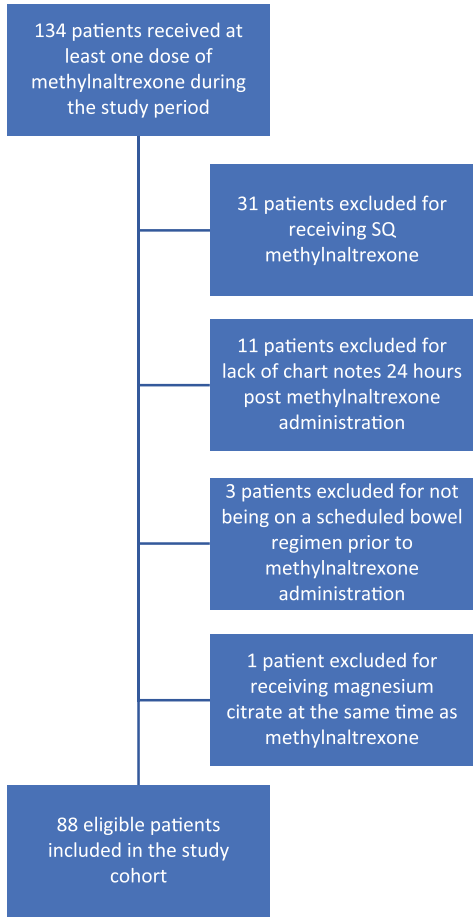

Table 1. Demographic and Clinical Characteristics of Patients

Characteristic	Value (n = 88)
Mean (SD) age, yr	9.5 (5.8)
Sex, n (%)	
Male	48 (55)
Female	40 (45)
Race, n (%)	
Black	11 (13)
Hispanic	7 (8)
Other	10 (11)
White	60 (68)
Underlying disease state, n (%)	
Oncology	68 (77)
Medical/surgical (i.e., non-oncology)	20 (23)
Mean (SD) number of unique bowel agents administered in 24 hr prior to methylnaltrexone*	1.7 (1.3)
Concurrent naloxone infusion, n (%)	44 (50)
Vinca alkaloids use in 30 days prior to methylnaltrexone dose, n/N (%)†	31/68 (46)

* Includes all formulations of bisacodyl, docusate, glycerin, lactulose, magnesium citrate, magnesium hydroxide, polyethylene glycol, senna, and sodium phosphate enemas.
† Among patients with oncology diagnosis.

or surgical conditions, including respiratory distress, sickle cell pain crisis, and postoperative ileus. Most of the patients in the study were white (68%), and the study population included more males than females (55% versus 45%, respectively).

Patients received an average of 1.7 unique bowel agents (Table 1) in the 24 hours preceding the methylnaltrexone dose. Of the study cohort, 44 patients (50%) were simultaneously receiving a continuous infusion of naloxone at the time of methylnaltrexone administration; these included 38 patients with an underlying oncology diagnosis and 6 patients with an underlying medical/surgical diagnosis. Of the patients with an oncology diagnosis, 31 (46%) had received a vinca alkaloid within the prior 30 days. A full list of patient demographics can be found in Table 1.

Response to Therapy. Table 2 provides a summary of the response rates with IV methylnaltrexone. Among the entire cohort, 25% (95% CI, 16–34) responded to their initial dose with a stool evacuation within 4 hours of methylnaltrexone administration. The response rate among oncology patients was 26% (95% CI, 16–37), which was not significantly different from the rate of 20% (95% CI, 2–38) among non-oncology patients (p = 0.56). Of the 44 patients receiving continuous infusion naloxone at the same time as methylnaltrexone administration, 27% (95% CI, 14–40) responded to the dose of methylnaltrexone, compared with a response rate of 23% (95% CI, 10–35) in patients not receiving concomitant continuous infusion naloxone (p = 0.62). Among the 31 oncology patients who received a vinca alkaloid within the previous 30 days, 13% (95% CI, 1–25) responded to a single dose of methylnaltrexone, compared with a response rate of 38% (95% CI, 22–53) in oncology patients who did not receive vinca alkaloids in the previous 30 days (p = 0.02).

Safety. In the study cohort, at least 1 adverse effect within the 24 hours following methylnaltrexone administration was documented in 38 patients (43%; 95% CI, 33–54). Among these 38 patients, a total of 64 adverse events were described. The most common adverse event reported was abdominal pain, at 25% (95% CI, 16–34). Nausea and vomiting were the next most common adverse events, occurring in 23% (95% CI, 14–34) and 16% (95% CI, 8–24) of patients, respectively. Among oncology patients specifically, rates of nausea and vomiting were 25% (95% CI, 15–35) and 16% (95% CI, 7–25), respectively, whereas among non-oncology patients, the rates for nausea and vomiting were both 15% (95% CI, 0–31).

Table 2. Response Rates

	Response Rate, % (95% CI)
Entire cohort	25 (16–34)
By diagnosis type	
Oncology patients (n = 68)	26 (6–44)
Medical/surgical patients (n = 20)	20 (16–37)
By concomitant naloxone infusion	
Yes (n = 44)	27 (14–40)
No (n = 44)	23 (10–35)
Received vinca alkaloid in prior 30 days*	
Yes (n = 31)	13 (4–30)
No (n = 37)	38 (22–53)

* Among patients with oncology diagnosis.

Table 3. Rates of Recorded Potential Adverse Reactions Following Intravenous Methylnaltrexone in our Pediatric Patients Relative to Rates Reported in the Package Insert for Subcutaneous Methylnaltrexone in Adult Patients

	Rate of Adverse Reactions, % (95% CI)*	Rate of adverse reactions per Package Insert, %
Abdominal pain	25 (16–34)	14–29
Nausea	23 (14–32)	9–12
Vomiting	16 (8–24)	2
Dizziness	3 (1–10)	7
Headache	3 (1–10)	4
Anxiety	1 (0–6)	2
Rhinorrhea	1 (0–6)	2

* Potential adverse reactions reported within 24 hours of methylnaltrexone administration

Rates of other reported adverse events in the study cohort are included in Table 3. Rare or serious adverse events, including gastrointestinal perforation, opioid withdrawal syndrome, or syncope, were not noted in the study cohort. Additionally, there was no reported reversal of analgesia in either subgroup, as identified in chart notes or based on an increased requirement of analgesic therapy. Naranjo scores identified only 3 adverse events classified as "possible ADR" and did not identify any adverse events classified as "probable ADR" or "definite ADR." These 3 possible ADRs included a single occurrence of abdominal pain, 1 of vomiting, and 1 of dizziness.

Discussion

In this retrospective, single-center study, we report the response rate and adverse event rate associated with IV methylnaltrexone use in pediatric patients. Our response rate was lower than that found in a systematic review by Nee et al,[18] who evaluated 6 randomized controlled trials in which adult patients (n = 1004) received oral, subcutaneous, or IV methylnaltrexone. Nee et al[18] found a 52% response rate to methylnaltrexone, compared with a 29% response rate in the placebo group. This was a high response rate in the placebo group, because other studies document a response rate with placebo between 7% and 18%.[5,19–21] The researchers found a higher response rate in patients with cancer-related pain (RR, 0.51; 95% CI, 0.41–0.63) compared with those treated with non–cancer-related pain with OIC (RR, 0.75; 95% CI, 0.63–0.90). The only study included within the review by Nee et al[18] that evaluated the efficacy of a single dose of subcutaneous methylnaltrexone identified a response rate, defined as defecation within 4 hours, of 62% in patients treated with a dose of 0.3 mg/kg, 58% in patients treated with a dose of 0.15 mg/kg, and 14% for patients treated with placebo ($p < 0.0001$).[22] Within the study by Nee et al,[18] there was significant heterogeneity among the studies included in the systematic review. The administration method of methylnaltrexone varied among groups, and definitions were not consistent among the studies. For example, there currently is no standard definition for OIC. Similarly, reported response rates to methylnaltrexone may vary considerably because the definition of treatment response is not consistent among studies. In our study, we defined response as a definitive bowel evacuation as noted by the physician or nurse, whereas other studies included increased bowel sounds, decreased abdominal girth, or a stool smear as a positive response to treatment. This likely contributed to our lower rate of response compared with other published data.

Our study was limited to evaluating a single dose of methylnaltrexone and did not include patients' subsequent doses. This was due to the fact that if a patient responded to the first dose, we would expect similar results if they required subsequent doses during the same hospitalization or in future hospitalizations. This would result in a higher response rate than would be expected for the general population. Alternatively, patients that did not respond to the initial methylnaltrexone dose were frequently given multiple additional bowel agents between methylnaltrexone doses. This additional variable was complicated to incorporate into the small sample size, so the decision was to omit subsequent doses entirely.

Only 3 described adverse events met the criteria of a possible adverse drug reaction using the Naranjo score tool. However, when compiling all potential adverse effects described in the provider and nursing notes our study identified a higher rate of reported

nausea and vomiting in the cohort treated with IV methylnaltrexone compared with the rate of nausea and vomiting reported in the methylnaltrexone package insert.[4] This is most likely because oncology patients who were receiving concomitant chemotherapy treatment made up a large proportion of our cohort, and chemotherapy itself has an extensive adverse reaction profile. The reported rates of adverse effects for methylnaltrexone within the package insert did not include any studies that only evaluated patients with an oncology diagnosis who were actively receiving chemotherapy. Thus, it is possible that the rates of nausea and vomiting are actually higher in this population secondary to chemotherapy exposure, explaining the rate of nausea and vomiting we identified in this patient population. Among non-oncology patients, rates of nausea were consistent with those on the package insert, and the rate of vomiting was elevated, but the CI did cover the package insert rates. Although the Naranjo scores did not indicate most of these adverse effects were directly due to methylnaltrexone, previous studies included in the package insert for methylnaltrexone did not indicate Naranjo scores were used when compiling the adverse effect profile of the medication. This may explain why the rates of adverse effects in this population of our study closely aligns with the rates of adverse effects listed in the package insert. The non-oncology subgroup was relatively small, so additional information is needed on rates of adverse events among this specific population. Outside of nausea and vomiting, rates of adverse reactions closely aligned with the adverse event profiles from the package insert for methylnaltrexone. Other common adverse reactions identified in the package insert were not seen in our cohort, including chills, hyperhidrosis, hot flashes, muscle spasms, and tremors.

One concern regarding the reported higher rates of nausea and vomiting in our cohort is that they were potentially symptoms of opioid withdrawal. However, further chart review of these patients revealed no increases in opioid requirements, no mention of opioid withdrawal concerns in the chart notes, and no additional symptoms of opioid withdrawal mentioned in the chart notes (i.e., tremors, chills, yawning, etc.).

A surprising result of this study was the response rate in patients who were simultaneously receiving continuous infusion naloxone. The use of low-dose continuous infusion naloxone (0.5–2 mcg/kg/hr) is a common practice at Children's Minnesota for patients receiving continuous infusion opioids, in an effort to reduce the incidence of opioid-induced adverse events, including nausea, itching, and constipation.[23] We would expect that patients currently on low-dose continuous-infusion naloxone would likely not respond to methylnaltrexone, because in theory this would be a duplication of treatment. However, our response rate in patients receiving continuous infusion naloxone was similar to that in the population not receiving continuous infusion naloxone.

Expectedly, we found a lower rate of response in patients who had received a dose of vinca alkaloids in the 30 days prior to methylnaltrexone administration. It is well understood that constipation related to the use of vinca alkaloids is due to autonomic neuropathy, which differs from OIC.[24] When constipation is due to autonomic neuropathy secondary to vinca alkaloid use, the response to laxatives is often diminished, with up to 40% of patients reportedly not experiencing improvement with laxative use.[25] Because the pathophysiology of autonomic neuropathy is different from that of OIC, we would not expect an opioid antagonist to alleviate constipation associated with vinca alkaloid use, and this would be demonstrated by a lower response rate with methylnaltrexone use in this patient cohort. This expectation was confirmed within our results.

This study has some limitations that must be addressed. First, this was a retrospective chart review, so the investigators were reliant on chart notes and laboratory values to determine each patient's response to treatment and reported adverse effects. Second, this is a single-arm study with no comparator group. Originally, we planned to compare this study cohort to pediatric patients who received subcutaneous methylnaltrexone; however, dramatic differences in the underlying disease states between the 2 cohorts did not allow for a critical comparison. Most of the patients that received IV methylnaltrexone were patients with an underlying oncology diagnosis, most of whom were receiving concomitant chemotherapy treatment. Thus, we could not compare the safety profile between the IV and subcutaneous groups because most of those receiving subcutaneous doses were patients with a medical or postoperative surgical indication outside of oncology and were not being treated with additional medications concomitantly that are highly associated with adverse events. The inability to account for these drastic differences in variables between these 2 groups did not allow for a direct comparison as originally planned.

Additionally, as previously mentioned, this study only evaluated the response rate and rates of adverse events following a single dose of IV methylnaltrexone. Previous studies in the adult population have evaluated multiple-dose regimens of IV methylnaltrexone and have not identified significant adverse events with the potential of drug accumulation, but this has not been confirmed in the pediatric population.[10,26] Also, while we attempted to account for bowel regimens prior to methylnaltrexone administration, our institution lacks a standard approach to bowel care. Because of this, patients differed in which bowel agents they were receiving and the doses prescribed for each agent. Although we were able to account for the number of scheduled bowel medications each patient was receiving prior to methylnaltrexone, the differences in which bowel agents each patient was receiving and their dosing are variables for which we were unable

to account. Lastly, we were unable to calculate the 24-hour oral morphine equivalent for each study patient. This value would have been beneficial in determining whether methylnaltrexone efficacy varied based on oral morphine equivalent. This was omitted because of limitations with our medical record and discrepancies in the literature for the oral morphine equivalent of certain opioids, including intravenous methadone, which many of the patients were receiving.

Conclusion

In the pediatric population, the administration of IV methylnaltrexone may serve as an alternative treatment option for OIC, specifically when other treatment options have failed and other administration routes may not be feasible. This study demonstrated lower response rates than previous studies, but it resulted in a bowel evacuation within 4 hours after administration for 25% of the study population experiencing refractory OIC. There was a higher rate of nausea and vomiting compared with the rates reported in the package insert for methylnaltrexone. Further studies are warranted to identify the most likely responders to this therapy, and consideration for the use of IV methylnaltrexone should be weighed on a case-by-case basis.

Article Information

Affiliations. Department of Pharmacy (MR, KG, ML), Children's Minnesota, Minneapolis, MN; Research Institute (DW) Children's Minnesota, Minneapolis, MN.

Correspondence. Mike Raschka, PharmD, BCPPS; mike.raschka@childrensmn.org

Disclosures. The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. MR and DW had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethical Approval and Informed Consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and have been approved by the appropriate committees at our institution (Children's Minnesota, Minneapolis, MN). All patients and/or parents/caregiver(s) provided written informed consent and/or assent (as applicable) at enrollment.

Acknowledgment. We thank Martin Cozza for comments and recommendations on the manuscript.

Submitted. June 25, 2023

Accepted. October 19, 2023

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