PEDIATRIC PHARMACOTHERAPY

UNIVERSITY of VIRGINIA Children's Hospital

Volume 22 Number 5 May 2016

Analgesics and Adjunctive Therapies in Pediatric Palliative Care
A Review of the Recent Literature

Marcia L. Buck, PharmD, FCCP, FPPAG

Appropriate use of medications to reduce pain and discomfort is an important component of pediatric palliative care. Growing interest in expanding the availability of palliative care and hospice services for children has led to a significant increase in the literature in this area.[1,2] Included in these papers are a number of articles describing the current state of medication use in pediatric palliative care, as well as new alternatives for providing sedation and analgesia and new methods of preventing or minimizing adverse drug effects.

Assessments of Medication Use

Several recent studies have documented a wide range of drugs used to optimize comfort in children in this setting. A recent 3-month observational study of 515 patients from six pediatric palliative care programs found an average of 9 medications used per patient, with a range from 0 to 18.[3] The patients ranged from newborns to 19 years of age, with the most common conditions being congenital or genetic syndromes (40.8%), neuromuscular disease (39.2%), cancer (19.8%), respiratory disease (12.8%), or gastrointestinal disease (10.7%). The most frequently given medications, used in at least 20% of patients, were acetaminophen, albuterol, lansoprazole, and lorazepam. Morphine was given in only 15% of children, possibly reflecting the high percentage of very young patients with congenital or genetic syndromes. Morphine use, as well as oxycodone (9%), methadone (4%), and fentanyl (3%) use was more common in the early (within 30-day) mortality group, suggesting the need for higher levels of analgesia with more rapidly progressing or more advanced disease. Other medications used in at least 10% of patients included antibiotics (16%), levetiracetam (15%), phenobarbital (15%), ranitidine (15%), ibuprofen (12%), polyethylene glycol 3350 (11%), and baclofen (11%).

A retrospective study of 70 pediatric patients with brain tumors receiving palliative care was published earlier this year in the *European Journal of Paediatric Neurology*.[4] The patients (mean age 11.5 years) included 43 patients with supratentorial tumors, 11 with intratentorial tumors, and 16 with brain stem tumors. The authors reported analgesia use in 84% of patients, with 54% requiring high-potency opioids. Twenty-five patients (36%) used patient-controlled analgesia (PCA). Dexamethasone was used in 39 patients (56%), with antiepileptics used in 33 (47%), and antiemetics in 32 (46%). Patients with supratentorial tumors were the most likely to require antiemetics and antiepileptics, and had seizures that were often refractory to commonly used therapies. They noted that sedation was rarely needed in this population and recommended that benzodiazepines be used only in patients with anxiety or agitation.

Alternative Methods for Drug Delivery

Intranasal administration of sedatives, analgesics and adjunctive therapies has been adopted by many programs to allow administration in patients no longer able to take medications orally and in whom placing IV access is not desired. In a 2013 review of 58 neonates and infants receiving comfort care, Harlos and colleagues described the use of intranasal fentanyl in eleven of the patients.[5] In all cases fentanyl was administered for signs of labored breathing and restlessness at the end of life. The mean initial dose was 1.3 mcg/kg. Doses were given every 5 to 10 minutes as needed until the patient appeared comfortable. Five patients were treated on the first day of life; the remaining patients

were treated between the ages of 28 to 197 days. Three patients were treated after withdrawal of mechanical ventilation, and one patient was treated at home. The average number of doses given was 4.5 (range 1-17). The authors concluded that intranasal fentanyl provided a minimally invasive and effective method of preventing distress in dying newborns and infants.

In an article just published in the *Journal of Palliative Medicine*, similar benefit was found with the administration of oral transmucosal medications in neonatal palliative care.[6] Drolet and colleagues evaluated their comfort care protocol using transmuscosal morphine (0.05 mg/kg) or midazolam 0.05 mg/kg, with transmucosal scopolamine (6 mcg/kg) or glycopyrrolate (6 mcg/kg) for excessive secretions resulting in worsening respiratory distress. Patients were assessed every 4 hours as well as 30 and 60 minutes after each medication dose with the Neonatal Pain, Agitation, and Sedation Scale (N-PASS). Twelve patients (median age 8 days, range 3-39) were included in the study. The median duration of protocol use was 2 days (range 0.5-22.5 days). Regular assessments were conducted 85% of the time; 64% of the as needed doses were followed by a reassessment within 1 hour. A mid-study questionnaire of the patients' nurses revealed 100% agreement with the statement that their patient's symptoms were relieved by administration of the transmucosal morphine or midazolam. Ninety-four percent of nurses would recommend the protocol to other institutions. Fentanyl was well tolerated, with mild apnea in 7 patients that did not require intervention.

Additional Choices for Sedation and Analgesia

Several recent papers have described the benefit of supplementing traditional opioids and benzodiazepines with newer agents. The use of combination therapy offers the potential for improved patient comfort and avoiding tolerance to opioids and benzodiazepines that can result in rapid dose escalation and dose-related adverse effects. Dexmedetomidine may be a useful choice. A frequently used sedative in pediatric intensive care, it provides analgesia without respiratory depression. It produces a light level of non-REM state sedation, a dose-dependent amnesia, and may reduce the development of delirium. It also acts as an anxiolytic and antisialagogue. The disadvantages of dexmedetomidine include the potential for bradycardia or other arrhythmias and hypotension.

In 2015, O'Hara and colleagues at Hershey Children's Hospital described the use of dexmedetomidine for sedation during withdrawal of ventilator support.[7] The patient was an adolescent girl with severe developmental delay, spastic quadriparesis, cortical blindness, renal disease, seizures, and chronic lung disease. She was admitted for the sixth time in the same year and required continuous bilevel positive airway pressure (BiPAP). After discussions with their daughter's medical team, the family chose not to pursue a tracheostomy and to discontinue respiratory support. At that time, she was receiving scheduled enteral lorazepam and morphine, with additional morphine as needed. After removal of the BiPAP she became progressively more tachypneic, and IV ketamine and midazolam were added to her regimen. The benefit was of a short duration and did not appear to the parents to being producing comfort. The addition of dexmedetomidine, at a rate of 0.4 mcg/kg/hr, produced comfort for 14 hours. At that point, she received several additional doses of morphine and midazolam and the infusion was increased to 0.7 mcg/kg/hr. The patient expired 10 hours later with no signs of distress.

Earlier this year, Gibbons and colleagues described the use of continuous lidocaine infusions in four pediatric and adolescent patients (ages 8-18 years) with terminal cancer and refractory pain.[8] Three patients had metastatic disease and one patient had neurofibromatosis type I with a malignant peripheral nerve sheath tumor. The patients received between one and eight treatment courses, with a loading dose of 1 mg/kg given in all but four courses. The initial dose ranged from 15 to 36 mcg/kg/min, with a final dosing range of 15-50 mcg/kg/min. The length of the infusions ranged from 4 hours to 17 days. All of the patients had received opioids (hydromorphone and/or methadone) and ketamine. Other pain therapies included diazepam or lorazepam, pregabalin, duloxetine, cannabinoids, and ibuprofen. One patient received dexmedetomidine.

Pain scores were significantly lower at 4 hours after initiation of lidocaine, compared to baseline ($p < 0.017$). Scores continued to decline during treatment and were still significantly lower than baseline 24 hours after discontinuing lidocaine ($p < 0.001$). Three patients experienced adverse effects potentially associated with lidocaine, including two with tingling or paresthesias and one patient with blurred vision and visual hallucinations. Symptoms resolved spontaneously or with dose reduction; none of

the adverse effects resulted in discontinuation of the infusion. Serum lidocaine concentrations were inversely related to pain scores, but did not correlate with infusion rates. All of the patients died within 19 months of their initial lidocaine infusion, with two receiving lidocaine at the time of death. The authors suggest that the unexpected duration of pain control experienced after completion of the infusion may result from additional mechanisms of action in long-standing pain states and conclude that lidocaine deserves further research in the treatment of opioid-refractory pain in the pediatric population.

Propofol has also been utilized in the pediatric palliative care setting. Anghelescu and colleagues at St. Jude Children's Research Hospital conducted a retrospective study of cancer patients who received propofol for palliative sedation within 20 days of their death.[9] Of the 192 patients evaluated over a 7-year period, only three had received propofol. The patients included a 9-year-old with angiosarcoma, a 6-year-old with neuroblastoma, and an 11-year-old with acute lymphoblastic leukemia. All three patients had experience multiple complications and were already receiving opioids at high doses. Propofol was initiated at 30 mcg/kg/min (1.8 mg/kg/hr) in the first patient and continued for 9 days until the patient's death. The second patient was placed on propofol at 30 mcg/kg/min after a period of rapid escalation of opioid PCA use failed to produce adequate pain relief. Use of propofol improved comfort while allowing a reduction in opioid and benzodiazepine doses. The patient died on the same day that propofol was started. The third patient also started propofol after an escalation of analgesia failed to resolve his grimacing and teeth clenching. His mother requested additional comfort measures and propofol was initiated at 60 mcg/kg/min (3.6 mg/kg/hr). He died on the third day of the infusion without needing any additional increases in his propofol, fentanyl, or midazolam infusion. The authors reported significant reduction in pain measures, improvements in sedation status, and a reduction in agitation and anxiety in the first two patients. The third patient was sedated prior to initiation of propofol and his resulting evaluations were unchanged; his mother noted that he appeared comfortable.

The authors also provided a review of previous reports and described their protocol for using propofol as a part of their palliative sedation therapy, addressing both its advantages and disadvantages. They caution that propofol use may result in respiratory depression, airway obstruction, hypotension, pain on injection, and potential infections from contamination of the product, or propofol infusion related syndrome. None of these adverse effects were noted in the three patients treated.

Antiepileptics

In observational and retrospective studies of pediatric palliative care programs, antiepileptics are used in 10-50% of patients.[3,4] Choice of drug often depends on both patient age and whether or not the drug is being used for seizure management or as an analgesic. Phenobarbital is frequently chosen for neonates and infants because of the familiarity with its use in this patient population and its beneficial sedative effects. Levetiracetam has been included in many of the recent descriptions of pediatric palliative care programs, reflecting its widespread use in pediatric epilepsy and the advantages it offers of a relatively mild adverse effect profile and few drug interactions in comparison to phenytoin or carbamazepine.[3] Gabapentin, although initially approved as an antiepileptic, is more often given for the management of neuropathic pain. In pediatric patients, it may be initiated at a dose of 5 mg/kg nightly with titration to a usual maintenance dose of 5 mg/kg three times daily or 5 mg/kg in the morning and 10 mg/kg at night.[1,2]

Antiemetics

Most palliative care patients receiving high dose opioid therapy will require antiemetics.[1-4,10,11] Ondansetron and other selective 5-hydroxytryptamine ($5\text{-}HT_3$) antagonists are frequently used in children. This class of drugs offers the advantages of a well-established safety and efficacy profile as well as the availability of parenteral and oral dosage forms, including oral solutions, suspensions, and orally disintegrating tablets. Dexamethasone and lorazepam are also effective antiemetics with additional therapeutic benefits. Metoclopramide 0.1-0.2 mg/kg up to three times daily or promethazine 0.25-0.5 mg/kg every 4 to 6 hours may be administered orally or rectally in children with nausea and vomiting not responsive to other therapies. Both drugs are sedating, which may or may not be beneficial, and may produce extrapyramidal effects which limit their utility in children.

Management of Constipation

Constipation is a common problem in patients with severe or chronic pain, resulting from opioid use as well as dehydration, poor nutritional intake, and immobility. Traditional therapies include hydration, stool softeners such as docusate sodium or glycerin, and laxatives such as polyethylene glycol 3350, senna, or bisacodyl.[2] Early use of these therapies is recommended, ideally before the point at which

the patient is receiving regular doses of high-potency opioids. Two new options have been approved by the Food and Drug Administration (FDA) for the management of opioid-induced constipation (OIC). Methylnaltrexone and naloxegol are opioid antagonists that compete with opioids at peripheral mu-opioid receptors without interfering with binding at central opioid receptors. Methylnaltrexone can be administered intravenously or subcutaneously; naloxegol is available as oral tablets. Neither product is currently approved by the FDA for use in children.

In 2013, Rodrigues and colleagues at The Hospital for Sick Children published the results of a retrospective study of 15 children (median age 14 years, range 4-17 years) with cancer treated with methylnaltrexone for OIC.[12] Patients received morphine, hydromorphone, or fentanyl at a median oral morphine dose equivalent of 5.7 mg/kg/day (range 1.5-29.2 mg/kg/day). All had received multiple laxatives. Twelve patients received a single subcutaneous methylnaltrexone dose of 0.15 mg/kg, while three were given multiple doses. A bowel movement occurred within 4 hrs after 14 of the 19 doses given. In 10 cases, the bowel movement happened within 30 minutes. There were no cases of reduced pain control or opioid withdrawal.

In a 2015 retrospective study published by Flerlage and Baker in the *Journal of Palliative Medicine*, methylnaltrexone was found to be a safe and effective treatment in children and adolescents with OIC.[14] The nine patients, ranging in age from 17 months to 21 years, had progressive incurable cancer and were treated with a methylnaltrexone dose of 0.15 mg/kg. Seven (78%) had relief of their constipation, five (71%) with a single dose. Of the patients given multiple doses, the longest treatment period was 9 months. In the five patients with intraabdominal disease, four responded. There were no adverse effects noted and no reports of loss of pain control or a change in pain scores.

There are currently no studies of naloxegol use in children, but a phase I open label multicenter pharmacokinetic and safety study is currently underway in children 6 months to 18 years of age. Details of the study are available at https://clinicaltrials.gov/ct2/show/NCT02099591?term=naloxegol&rank=2.

Summary

The growing recognition of the benefits of palliative care services for children has led to a number of new papers describing methods for improving pain control and minimizing patient discomfort. These papers, mostly small observational or retrospective studies, are valuable additions to the literature. Additional studies continue to be needed to confirm the utility of several of these new agents and new dosing techniques in order to optimize their use in the pediatric palliative care setting.

The author and editors would like to thank Dr. Noreen Crain for serving as our guest editor for this issue.

References

1. Downing J, Jassal SS, Mathews L, et al. Pediatric pain management in palliative care. Pain Manage 2015;5:25-35.
2. Komatz K, Carter B. Pain and symptom management in pediatric palliative care. Pediatr Rev 2015;36:527-33.
3. Feudtner C, Kang TI, Hexem KR, et al. Pediatric palliative care patients: a prospective multicenter cohort study. Pediatrics 2011;127:1094-101.
4. Kuhlen M, Hoell J, Balzer S, et al. Symptoms and management of pediatric patients with incurable brain tumors in palliative home care. Eur J Paediatr Neurol 2016;20:261-9.
5.Harlos MS, Stenekes S, Lambert D, et al. Intranasal fentanyl in palliative care of newborns and infants. J Pain Symptom Manage 2013;46;265-74.
6. Drolet C, Roy H, Laflamme J, et al. Feasibility of a comfort care protocol using oral transmuscosal medication delivery in a palliative neonatal population. J Palliative Med 2016;19:Epub ahead of print. DOI: 10.1089/jpm.2015.0045.
7. O'Hara C, Tamburro RF, Ceneviva GD. Dexmedetomidine for sedation during withdrawal of support. Palliative Care Res Treat 2015;9:15-8.
8. Gibbons K, DeMonbrun A, Beckman EJ, et al. Continuous lidocaine infusions to manage opioid-refractory pain in a series of cancer patients in a pediatric hospital. Pediatr Blood Cancer 2016;Epub ahead of print. DOI 10.1002/pbc25870.
9. Anghelescu DL, Hamilton H, Faughnan LG, et al. Pediatric palliative sedation therapy with propofol: recommendations based on experience in children with terminal cancer. J Palliative Med 2012;15:1082-90.
10. Korzeniewska-Eksterowicz A, Przyslo L, Fendler W, et al. Palliative sedation at home for terminally ill children with cancer. J Pain Symptom Manage 2014;48:968-74.
11. Vallero SG, Lijoi S, Bertin D, et al. End-of-life care in pediatric neuro-oncology. Pediatr Blood Cancer 2014;61;2004-11.
13. Rodrigues A, Wong C, Mattiussi A, et al. Methylnaltrexone for opioid-induced constipation in pediatric oncology patients. Pediatr Blood Cancer 2013;60:1667-70.
14. Flerlage JE, Baker JN. Methylnaltrexone for opioid-induced constipation in children and adolescents and young adults with progressive incurable cancer at the end of life. J Palliative Med 2015;18:631-3.