Dexmedetomidine-Associated Fever in a Critically Ill Obese Child

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Dexmedetomidine use in the pediatric intensive care unit has increased in recent years. Reports of dexmedetomidine-associated drug fever have been described in adult patients; however, this has not been reported in the pediatric population. We report a case of persistent fever that resolved with the discontinuation of dexmedetomidine and successful transition to clonidine. This is the first report of dexmedetomidine drug fever in a pediatric patient.

ABBREVIATION PICU, pediatric intensive care unit

KEYWORDS adverse drug effect; critical care; dexmedetomidine; drug fever; pediatric

J Pediatr Pharmacol Ther 2018;23(6):486–489

DOI: 10.5863/1551-6776-23.6.486

Introduction

Ensuring the safety and comfort of critically ill infants and children supported by mechanical ventilation is an integral part of pediatric critical care.¹ Dexmedetomidine is an intravenous, α_2 adrenergic-receptor agonist that acts centrally in the locus ceruleus to produce sedation.² Although dexmedetomidine is not approved for use in children by the US Food and Drug Administration, its use in pediatric critical care has grown in recent years.^{3,4}

The most commonly reported adverse effects of dexmedetomidine are hypotension and bradycardia.² Occurrence of fevers has been reported in the adult literature with dexmedetomidine and within the package insert.^{2,5,6} Fever in the pediatric intensive care unit (PICU) can lead to investigation of infectious processes via cultures, laboratory tests, and initiation of antimicrobial therapy. Ultimately, this can lead to inappropriate exposure to antibiotics and potential for adverse reactions, resistance development, and increased medical costs. Recognition of other causes of fevers, including drug-induced fevers, can lead to appropriate interventions, decreased antibiotic exposure, and decreased medical costs.

We report on a pediatric patient who developed a persistent low-grade fever during his PICU admission concomitant with the administration of dexmedetomidine. This resolved when the patient was successfully transitioned to enteral clonidine. Previous reports are reviewed and the approach to such patients is presented.

Case Report

Institutional review board approval is not required for presentation of single case reports at Nationwide

Children's Hospital. The patient was a 7-year-old male admitted to our facility's PICU after he received sedation for magnetic resonance imaging and required non-invasive positive pressure ventilation after the procedure because of persistent hypoxemia. His past medical history was significant for cervicomedullary pilocytic astrocytoma status after partial resection as well as chemotherapy and radiation, hypertension, hypoventilation with central sleep apnea, adrenal insufficiency, and morbid obesity. At admission, this child weighed 88.9 kg and had a body mass index of 59.7 kg/m². His ideal body weight was calculated at 24.6 kg, and medications were based on an adjusted body weight of 40 kg because of the patient's morbid obesity. He had a nocturnal bilevel positive airway pressure requirement prior to his admission to the PICU. At the time of admission, his home medications included albuterol inhaler as needed, clonidine 0.2 mg/24 hr transdermal patch once a week, fluticasone-salmeterol inhaler twice daily, isradipine 3 mg as needed for hypertension, sertraline (50 mg daily), and a multivitamin daily. Approximately 1 month prior to admission, he was receiving active oral chemotherapy of vemurafenib (480 mg twice daily) and was scheduled to start trametinib (2 mg daily); however, this had not been initiated at the time of admission.

Upon arrival to the PICU, he was initiated on bilevel positive airway pressure and his home medications were continued. On the second day of PICU admission, he developed a fever of 38.4°C via axillary measurement, and an infectious disease evaluation was started. His chest radiograph revealed an infiltrate, which was concerning for pneumonia. Antibiotic coverage was started, including cefepime (2000 mg intravenous every 8 hours), amikacin (450 mg intravenous every 8 hours), and vancomycin (1200 mg intravenous every

Figure. Temperature curve and dexmedetomidine infusion dose.

— Temperature; — Dexmedetomidine dose

PICU, pediatric intensive care unit.

6 hours), consistent with our institution's high-risk antimicrobial policy.⁷ On the fourth day of the PICU admission, his trachea was intubated secondary to worsening hypoxemia and increased work of breathing. High-frequency oscillatory ventilation was initiated, and sedation was provided by continuous infusions of fentanyl (150 mcg/hr) and midazolam (1.25 mg/hr). Neuromuscular blockage was initiated by an infusion of vecuronium (0.1 mg/kg/hr). Antibiotic therapy was de-escalated after 72 hours, and he completed a total of 10 days of cefepime for treatment of pneumonia; however, respiratory, urinary, and blood cultures were negative and the patient remained afebrile. The patient continued to require high-frequency oscillatory ventilation settings throughout this time period.

The patient had escalating sedation requirements throughout his first week on mechanical ventilation. On day 8 of PICU admission (day 5 of mechanical ventilation) escalating requirement of opioids and benzodiazepines necessitated the use of dexmedetomidine (Hospira Inc, Lake Forest, IL). Dexmedetomidine was dosed using an adjusted weight, and the infusion was started at 0.4 mcg/kg/hr. During the next 7 days, his sedation requirements were titrated to a goal sedation of ~ 3 using the State Behavioral Scale.⁸ Dexmedetomidine was continued and titrated to a maximum dose of 1.2 mcg/kg/hr during the PICU stay.

Starting on day 17 of PICU admission (day 15 of mechanical ventilation), the patient developed a low-grade fever of 38°C via axillary measurement secondary to suspected urinary tract infection, and cefepime was restarted. During days 18 through 21 of PICU admission, he continued to have intermittent low-grade fevers with a maximum temperature of 38.2°C (Figure). Cefepime was discontinued on day 20 of admission, and the in-

fectious evaluation remained negative. Other causes of fever were investigated, including d-dimer and a chest computerized tomography to evaluate for pulmonary embolism or thrombus around central line. The chest computerized tomography scan was negative, and D-dimer was only slightly elevated at 0.64 mg/L (reference: <0.5 mg/L). Lower extremity ultrasound also ruled out deep vein thrombosis.

On day 22 of PICU admission the patient had an acute increase in temperature to a maximum 38.6°C and had an increased oxygen requirement. Antibiotic therapy was initiated with cefepime (2000 mg intravenous every 8 hours), amikacin (1250 mg intravenous every 24 hours), vancomycin (1000 mg intravenous every 8 hours), and micafungin (100 mg intravenous every 24 hours) because of suspicion of ventilator-associated pneumonia, and an infectious disease consult was requested. The patient's C-reactive protein was 1.1 mg/dL (reference: < 1.2 mg/dL) and procalcitonin was <0.5 ng/mL (reference: < 0.5 ng/mL). He was continued on the antibiotics for 72 hours, when it was determined that the persistent fevers were not related to any infectious process. The antibiotics were discontinued in accordance with the recommendations of the pediatric infectious disease consultant. Ultimately, the respiratory culture grew coagulase-negative *Staphylococcus* and a *Candida* species, which were determined to be contaminants and not true infectious processes.

An exhaustive review of current medications was completed on day 25 of PICU admission (Table). Because of the persistent fever and review of literature regarding the incidence of hyperthermia with dexmedetomidine, it was decided to titrate off the dexmedetomidine infusion and initiate enteral clonidine at a dose of 200 mcg per the feeding tube every 8 hours.

Table. List of Medications at the Time of Persistent Fever

Continuous infusion medications

Dexmedetomidine 1.2 mcg/kg/hr continuous IV infusion
 Midazolam 2 mg/hr continuous IV infusion
 Morphine 20 mg/hr continuous IV infusion
 Naloxone 0.75 mcg/kg/hr continuous IV infusion

Scheduled medications

Albuterol 2.5 mg inhalation every 6 hr
 Artificial tears ophthalmic ointment applied to eyes every 4 hr
 Dornase α 2.5 mg inhalation every 12 hr
 Furosemide 10 mg IV every 8 hr
 Methadone 5 mg per feeding tube every 6 hr
 Multivitamin with iron 10 mL per feeding tube once daily
 Ranitidine 75 mg per feeding tube twice daily
 Sennosides 8.8 mg per feeding tube twice daily
 Sertraline 50 mg per feeding tube twice daily
 Sodium chloride 20 mEq per feeding tube every 6 hr
 Sodium chloride 3% aerosol inhalation twice daily

As-needed medications

Chloral hydrate 1000 mg per feeding tube every 6 hr
 Hydralazine 8 mg IV every 8 hr for hypertension
 Isradipine 3 mg per feeding tube every 6 hr for hypertension
 Midazolam 2 mg IV every hour as for sedation
 Morphine 20 mg IV every hour for pain or sedation
 Polyethylene glycol 17 g per feeding tube twice daily

IV, intravenous

Dexmedetomidine was decreased by 50% after the second dose of clonidine and discontinued after the fourth dose of clonidine. The patient's fever curve can be seen in the Figure.

After discontinuation of the dexmedetomidine infusion, the patient remained afebrile during the remainder of his PICU admission. On day 35 of PICU admission the patient underwent tracheostomy placement because of an inability to wean from mechanical ventilation and to facilitate PICU liberation. During placement of a tracheostomy, he received dexmedetomidine at a dose of 1 mcg/kg/hr for approximately 2 hours in the operating room. During this time he did not experience repeat fever. Ultimately, the patient was discharged from the PICU on day 41 of admission. After PICU discharge, he spent 5 weeks undergoing inpatient pulmonary rehabilitation and was eventually discharged home.

Discussion

Dexmedetomidine use is becoming increasingly common in the PICU, both for patients treated with

invasive and non-invasive ventilation.^{3,4} As such, it is important to recognize potential side effects of this medication, both those commonly encountered and those that are rarer. Fever in the critically ill patient always causes careful consideration because these patients are at high risk of nosocomial infection owing to multiple invasive devices and suppressed immune systems.

Unfortunately, these patients often have other causes of fever (e.g., venous thromboembolism, drug withdrawal) that can obscure their clinical pictures. During a prolonged PICU hospitalization, these patients are also likely to be treated with several courses of antibiotics, placing them at risk for such things as bacterial resistance and *Clostridium difficile* infection. Thus, recognizing other potential causes of fever is critically important.

Faust and Sutton⁵ describe an adult patient who began to have temperatures $>38^{\circ}\text{C}$ at approximately 24 hours after initiation of dexmedetomidine infusion. The patient developed persistent fevers greater than 39°C until discontinuation of the dexmedetomidine infusion, after which she rapidly defervesced with no other apparent cause of fever.

One of the first descriptions of dexmedetomidine-induced fever came in 2009 from Okabe et al,⁹ who described a similar case of an adult who developed fever approximately 22 hours after initiation of dexmedetomidine and rapidly defervesced after discontinuation. Most recently, Kruger et al⁶ described 9 adults in the cardiac intensive care unit who developed fever thought to be secondary to dexmedetomidine administration. These patients developed hyperthermia a median of 6 hours after initiation of dexmedetomidine and quickly returned to baseline after discontinuation of the infusion. Again, despite other workup, these patients had no obvious cause of fever.

Our patient demonstrated persistent high fever during dexmedetomidine administration and rapid defervescence with discontinuation of the dexmedetomidine infusion. He was transitioned to enteral clonidine without further fever. Infectious etiology and other causes of hyperthermia were excluded. Ours is the first pediatric patient described in the literature to have hyperthermia associated with dexmedetomidine; however, our patient was of adult weight. Based on the information presented in the case, we would assign a Naranjo score of 5, making it a probable adverse reaction to dexmedetomidine.¹⁰ Because the patient had been exposed to dexmedetomidine in previous admissions and re-exposed when his tracheostomy was placed, we were unable to link fever with the patient's other exposures to dexmedetomidine. This contributes to a lower score on the Naranjo scale.

Although the discontinuation of dexmedetomidine and transition to clonidine assisted with this patient's fever and infectious/hematology etiologies were ruled

out, other explanations for persistent fever in this patient exist. The patient was also receiving other medications that cause drug fevers, such as furosemide.^{11–13} Fevers can be associated with the administration of many medications, but we targeted continuous infusion medications because of the persistent nature of the fever. After successful defervescence of the patient, other medications were eliminated as causes of fever because these were continued throughout his admission.

Conclusion

We present the first pediatric case of probable hyperthermia associated with dexmedetomidine infusion. Our case closely echoes those of previous adult cases, including persistence of fever and rapid resolution of hyperthermia after discontinuation of dexmedetomidine. Further investigation into the etiology of fever associated with dexmedetomidine is warranted. As dexmedetomidine use becomes increasingly common in PICUs, recognition of the association with fever will be increasingly pertinent to the pediatric intensive care team.

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Disclosure 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. The authors had full access to all patient information in this report and take responsibility for the integrity and accuracy of the report.

Accepted April 2, 2018

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REFERENCES

1. Kudchadkar SR, Yaster M, Punjabi NM. Sedation, sleep promotion, and delirium screening practices in the care of mechanically ventilated children: a wake-up call for the pediatric critical care community. *Crit Care Med*. 2014;42(7):1592–1600.
2. Precedex [package insert]. Lake Forest, IL: Hospira Inc; June 2013. Accessed October 6, 2017.
3. Grant MJ, Schneider JB, Asaro LA, et al. Dexmedetomidine use in critically ill children with acute respiratory failure. *Pediatr Crit Care Med*. 2016;17(12):1131–1141.
4. Venkatraman R, Hungerford JL, Hall MW, et al. Dexmedetomidine for sedation during noninvasive ventilation in pediatric patients. *Pediatr Crit Care Med*. 2017;18(9):831–837.
5. Faust AC, Sutton SE. Dexmedetomidine-associated fever in the intensive care unit. *Ther Adv Drug Saf*. 2015;6(6):234–237.
6. Kruger BD, Kurmann J, Corti N, et al. Dexmedetomidine-associated hyperthermia: a series of 9 cases and a review of the literature. *Anesth Analg*. 2017;125(6):1898–1906.
7. Karsies TJ, Sargel CL, Marquardt DJ, et al. An empiric antibiotic protocol using risk stratification improves antibiotic selection and timing in critically ill children. *Ann Am Thorac Soc*. 2014;11(10):1569–1575.
8. Curley MA, Harris SK, Fraser KA, et al. State Behavioral Scale: a sedation assessment instrument for infants and young children supported on mechanical ventilation. *Pediatr Crit Care Med*. 2006;7(2):107–114.
9. Okabe T, Takeda S, Akada S, et al. Postoperative intensive care unit drug fever caused by dexmedetomidine. *Anesth Analg*. 2009;108(5):1589–1591.
10. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30(2):239–245.
11. Amir J, Varsano I. Furosemide-associated fever. *J Pediatr*. 1996;128(1):163–164.
12. Kavanagh GM, Warwick JA, Burton JL. Ranitidine fever. *Lancet*. 1993;341(8857):1422.
13. Zoloff [package insert]. New York, NY: Pfizer Inc; December 2016. Accessed October 6, 2017.