Posterior Reversible Encephalopathy Syndrome as a Result of Withdrawal from Prolonged Dexmedetomidine

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Abstract

Keywords

- ▶ posterior reversible encephalopathy syndrome
- ▶ dexmedetomidine
- ▶ withdrawal

Dexmedetomidine is a selective α -adrenergic agonist with high α -2 receptor affinity that is used for sedation, analgesia, and as an anxiolytic. Withdrawal symptoms, although rare, include agitation, irritability, headache, and rebound hypertension, which can occur following abrupt cessation of the medication. Posterior reversible encephalopathy syndrome is a clinical condition presenting secondary to acute hypertension that results in neurologic symptoms including headache, seizures, altered sensorium, and loss of vision. These symptoms are coupled with typically reversible characteristic magnetic resonance imaging changes. We present the first reported case of posterior reversible encephalopathy syndrome after a hypertensive crisis likely precipitated by dexmedetomidine withdrawal.

Introduction

Dexmedetomidine functions as a centrally acting α -2 adrenergic agonist. Its structure is similar to clonidine but it exhibits higher affinity for α -2 receptors than α -1 receptors at 1600:1, compared with clonidine (200:1). Dexmedetomidine additionally has a short-acting half-life of $\sim$ 2 hours, which makes it ideal for sedative effects with less concern for adverse reactions and withdrawal symptoms.¹ With good efficacy and safety profiles in adults, the utility of dexmedetomidine in the pediatric population for sedative effects has surged, though this is an off-label use.

Dexmedetomidine has a safety profile that is advantageous in the intensive care unit (ICU) setting for sedation needs. The main adverse effects noted include hypotension and bradycardia without any noted respiratory depression.² These side effects appear to be dose related, with resolution following dose reduction and intravenous fluid administration. These effects can be potentiated by concurrent use of medication with similar side effect profiles. With a structure similar to clonidine, abrupt discontinuation of dexmedetomidine may cause similar withdrawal symptoms. Clonidine is

known to have withdrawal side effects including nervousness, agitation, headache, and rebound hypertension following its discontinuation.³ Retrospective studies examining prolonged use of dexmedetomidine therapy have demonstrated few adverse events following its discontinuation.^{4–7} We present a case report of an 11-year-old girl with a history of sickle cell disease that developed posterior reversible encephalopathy syndrome (PRES) secondary to hypertension following the abrupt cessation of a prolonged dexmedetomidine infusion.

Case Report

An 11-year-old (35 kg) African American female with known history of hemoglobin SS disease presented to the emergency department with chest pain that had been worsening in intensity over 1 day's duration. Upon arrival in the emergency department, she appeared to be in respiratory distress with an altered mental status. Initial vital signs documented severe hypoxia. A chest X-ray obtained showed opacification of her right lung field concerning for acute chest. She was

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emergently intubated and placed on synchronized intermittent mandatory ventilation with continuous infusions of fentanyl (2 µg/kg/h) and midazolam (0.1 mg/kg/h) for sedation. Due to her respiratory status and severe anemia/sickle crisis, the patient required an exchange transfusion on hospital day 2. She also received packed red blood cell transfusions on days 2 and 3. She additionally required dopamine, titrated between 2 and 20 µg/kg/min, and norepinephrine, titrated between 0.01 and 0.3 µg/kg/min, for blood pressure support. Dopamine and norepinephrine were discontinued once the patient established appropriate blood pressures on hospital day 3.

Dexmedetomidine therapy was initiated on hospital day 2 with starting dose of 1 µg/kg/h to provide additional sedation while intubated with the goal of discontinuing the midazolam infusion.

The patient's respiratory status improved and she was extubated to room air on hospital day 9. Following extubation, fentanyl, current dose of 2.2 µg/kg/h, and dexmedetomidine, current dose of 0.7 µg/kg/h, infusions were discontinued. Patient had received a cumulative dose of 167.376 µg/kg and 160 hours of infusion of dexmedetomidine prior to its discontinuation. The patient continued to receive fentanyl 20 µg boluses every 2 hours for pain and midazolam 2 mg every 8 hours as needed for agitation following extubation and discontinuation of continuous sedatives.

On the evening of hospital day 9, ~15 hours following extubation, the patient's blood pressure was noted to be elevated with systolic blood pressures ranging from 140 to 170 mm Hg (95th percentile for her height was >107 mm Hg) and diastolic blood pressures ranging from 80 to 105 mm Hg (95th percentile for her height was > 63 mm Hg). She was also noted at the time to be increasingly restless, agitated, and combative upon examination. Blood pressures were presumed to be falsely elevated secondary to patient's agitation. She received lorazepam with noted improvement in blood pressure and agitation.

The following day there was concern that her persistent agitation and elevated blood pressure were secondary to medication withdrawal. Continuous dexmedetomidine infusion at 0.6 µg/kg/h and fentanyl at 3.0 µg/kg/h were restarted. Her blood pressure remained elevated, so the decision was made to initiate therapy with nicardipine. Infusion of nicardipine was started at 0.5 µg/kg/h. At the time of the nicardipine initiation, the patient's blood pressure had been elevated for age at > 130/70 for 13 hours in duration. The patient was also noted to have continued tachypnea with grunting on physical exam, so she was electively reintubated.

Later that evening the patient experienced two episodes of brief seizure-like activity with generalized twitching, each occurrence lasting less than 1 minute. The morning of hospital day 11, the patient was noted to have altered mental status, decreased responsiveness, and dysconjugate gaze on examination. Dexmedetomidine, at 0.7 µg/kg/h, and fentanyl, at 2.2 µg/kg/h, continuous infusions were discontinued to allow for further evaluation of mental status. An urgent head computed tomography and electroencephalography (EEG) were obtained at that time. The computed tomography

scan did not reveal any significant abnormalities apart from minimal sinusitis, while the EEG demonstrated generalized seizure activity. She was started on a midazolam infusion at 0.2 mg/kg/h and was loaded with and maintained on levetiracetam for seizure control. A continuous EEG was initiated, which noted cessation of seizure activity ~2 hours following levetiracetam loading dose and midazolam continuous infusion. Dexmedetomidine was again restarted at 0.5 µg/kg/h as well as fentanyl at 2 µg/kg/h to provide sedation. A head magnetic resonance imaging obtained that evening demonstrated findings consistent with PRES.

The patient was continued on sedation and seizure control with continuous infusions of midazolam, fentanyl, and dexmedetomidine, while strict blood pressure control was maintained. A clonidine patch of 0.3 mg/day was placed to maintain a systolic blood pressure of less than 100 mm Hg, and the nicardipine was slowly weaned. Labetalol, hydralazine, and amlodipine therapy were eventually added to maintain systolic blood pressures between 90 and 100 mm Hg. Her dexmedetomidine was weaned by 0.1 µg/kg/h every 3 to 4 hours over the course of 2 to 3 hours with complete discontinuation occurring on hospital day 13. She remained on midazolam and fentanyl continuous infusions following discontinuation of dexmedetomidine. Midazolam was weaned by 0.05 mg/kg/h every 4 to 6 hours and then discontinued following extubation to nasal cannula on hospital day 14. Upon discontinuation of midazolam infusion, a scheduled dose of lorazepam 1 mg every 8 hours was provided to help mitigate withdrawal symptoms. Her lorazepam dosage was subsequently weaned and eventually discontinued on hospital day 17. Her fentanyl infusion was weaned by 0.2 µg/kg/h prior to its discontinuation on hospital day 19.

The patient's neurologic status demonstrated slow improvement, demonstrating minimal response to commands and verbalization on hospital day 17. She was transferred out of the ICU setting on hospital day 21 to an inpatient ward once she no longer required as needed medications for hypertension. Her antihypertensive doses were adjusted to maintain stable blood pressure control requiring amlodipine 7.5 mg orally daily and clonidine patch 0.1 mg at time of discharge. The patient continued to struggle with self-cares including mobility, ambulating independently, feeding herself independently, and controlling bowel and bladder function as well as delayed cognition. At the time of discharge, the patient demonstrated improved ability to care for herself but continued to struggle with balance, particularly navigating a safe route between two points, as well as demonstrating significant cognitive deficits below baseline. She was discharged home on hospital day 32 to an outpatient daily rehabilitation facility for continued rehabilitative services.

Discussion

Dexmedetomidine is a selective α-adrenergic agonist with a high α-2 receptor affinity approved by the Food and Drug Administration in December 1999 for use in the sedation of adults that are mechanically ventilated in the ICU for use less than 24 hours.² With success and demonstrating a good

safety profile in the adult population, dexmedetomidine has been utilized for years in pediatric patients for both short- and long-term sedation purposes. The use of dexmedetomidine in children is promoted by the desire to reduce opioid and benzodiazepine use, and their subsequent withdrawal symptoms, in sedation and analgesia in the ICU setting. In a review of the use of dexmedetomidine in pediatric patients, Buck determined that effective doses of dexmedetomidine in children were similar to adult patients with recommendations of dosing range of 0.2 to 0.7 $\mu\text{g/kg/h}$. It was recommended that this dosage be titrated in pediatric patients with both their age and clinical status in mind.²

However, a study looking at the utilization of dexmedetomidine for sedation in adult ICU settings found that medically ill patients required higher continuous infusion doses for adequate sedation compared with their postoperative counterparts. A ceiling effect was additionally noted at 1.5 $\mu\text{g/kg/h}$ without improved efficacy exhibited beyond this dosage.⁸ This study only utilized adult patients but one could presume that this may be extrapolated for use in the pediatric population. Our particular patient required higher doses of dexmedetomidine infusions to maintain sedation without needing to additional sedative agents to achieve adequate sedation.

Withdrawal symptoms of abrupt dexmedetomidine discontinuation, while rare in many studies and reports, have been shown to include agitation, irritability, headaches, tachycardia, and rebound hypertension. Limited data discussing withdrawal in the pediatric population are now becoming available. In a study reviewing discontinuation of continuous dexmedetomidine infusion in a 2-year-old boy following cardiac surgical repair, the patient was noted to exhibit blank staring episodes, agitation, and decreased verbal communication skills with asymmetrical pupils 5 hours following the discontinuation of dexmedetomidine therapy. He continued to receive methadone and diazepam at the same doses prior to dexmedetomidine. This male patient's neurologic status improved 2 days following abrupt onset after receiving as needed doses of lorazepam and morphine. The authors concluded that when discontinuing dexmedetomidine therapy after prolonged use, the dose should be tapered by 0.1 $\mu\text{g/kg/h}$ over a 12- to 24-hour period. They recommended that the patient should further be monitored for 12 to 23 hours following discontinuation to observe for any symptoms concerning withdrawal.⁹

An additional case report discussed a patient that developed transient neurologic abnormalities including facial droop and decreased verbal communicative skills following discontinuation of dexmedetomidine following 11 days of continuous infusion. This patient's dexmedetomidine infusion was stopped abruptly without a taper or dose reduction.³

These two cases demonstrate some of the possible neurologic consequences following discontinuation of dexmedetomidine therapy. In our case report, the patient developed severe neurologic sequela in the form of PRES correlating directly with the abrupt discontinuation of dexmedetomidine therapy. PRES, also termed reversible posterior leukoencephalopathy, is a condition classically characterized by seizure

activity, headaches, acute onset of encephalopathy, and visual disturbances.¹⁰

In a review of literature related to the pediatric population with PRES syndrome, the authors found that of 108 children who suffered from PRES, 92 (85%) had hypertension at the onset of disorder. This may be attributed to pediatric patients' cerebrovascular system being more sensitive to hypertensive conditions.¹¹ These findings are similar to study findings looking at sickle cell patients who developed PRES that found 89% of those patients experienced hypertension at the onset of PRES.¹²

Though most individuals with PRES have an uncomplicated course, there are known life-threatening complications of this disorder. The most commonly seen life-threatening complications include status epilepticus, cerebral hemorrhage, and cerebellar herniation. In reviewing literature, one study found that as many as 18% of patients who experienced PRES went on to develop one of these life-threatening complications.¹³ Therefore, developing PRES places patients at risk of not regaining previous neurologic functioning.

Our patient's rebound hypertension started within 12 to 15 hours of cessation of dexmedetomidine with neurologic disturbance shortly following. She received 160 hours of total dexmedetomidine infusion with a cumulative dose of 167.376 $\mu\text{g/kg}$. She additionally progressed to seizure activity shortly following onset of hypertension, which resolved with levetiracetam and tight blood pressure control with nifedipine. While it is difficult to correlate the seizure activity directly with the cessation of dexmedetomidine and instead it correlates more with the patient's PRES syndrome, the abrupt discontinuation of dexmedetomidine therapy seemed to be the inciting factor in hypertension leading further to seizures associated with PRES.

With the slow taper of dexmedetomidine and the addition of the clonidine patch, as well as the control of the patient's blood pressure with the nifedipine infusion, the patient has had a slow recovery of baseline function. With this case showing more long-lasting neurologic sequela secondary to an acute hypertensive episode, it is important to understand the danger of abruptly discontinuing dexmedetomidine following prolonged therapy, as well as the potential association of dexmedetomidine withdrawal with PRES.

In conclusion, dexmedetomidine is a medication for sedation and analgesia that is used in the pediatric population to decrease opioid and benzodiazepine reliance and overuse. Due to its short half-life, we recommend good hemodynamic and neurologic monitoring during use as well as continuing for 12 to 24 hours after cessation much like previous authors describe. We also recommend a standard tapering dose for those patients on prolonged (>24 hours) therapy before discontinuation or switching to an alternative medication and weaning, such as clonidine, which has a similar structure and biochemical function. Our current adapted clinical practice now includes placement of a clonidine patch 24 hours prior to initiation of dexmedetomidine taper and a slow taper of this medication to minimize the risk of withdrawal side effects. With recent implementation of this protocol in our

clinical setting, additional studies would be beneficial to determine the most appropriate weaning protocol to negate potential withdrawal side effects, not only hemodynamic effects but also neurologic sequel.

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