Dexmedetomidine (Precedex®, Hospira) is a selective alpha-2 adrenergic agonist with sedative, analgesic, and anxiolytic effects. It was initially approved by the Food and Drug Administration in 1999 for sedation in mechanically ventilated adult patients, for periods less than 24 hours. In addition to its sedative effects, it also possesses mild analgesic and anxiolytic properties coupled with minimal respiratory depression.1

Use in pediatrics is currently off label, consistent with the use of many other sedatives in this patient population. Nonetheless, it has seen increasing usage in the past few years, primarily in procedural sedation. It is also used for sedation in mechanical ventilation and clinical situations requiring longer term sedation. Adult studies have also demonstrated utility as a narcotic sparing agent in postsurgical patients.2

Dosing regimens for dexmedetomidine are not well defined in pediatric patients. Limited data suggest that a suitable range is 0.1–2.0 mcg/kg/hr.3 Other publications have documented doses as high as 2.7 mcg/kg/hr.4,5

Adrenal crisis is a syndrome that occurs either with acute onset adrenal insufficiency or in a patient with chronic adrenal insufficiency who experiences significant physiologic stress. The syndrome is usually associated with deficiencies in both mineralocorticoids (eg, aldosterone) and glucocorticoids (eg, cortisol), but can also be partial. The most dangerous issues are caused by mineralocorticoid deficiency—hyponatremia, hyperkalemia, metabolic acidosis, and hypotension. Acute drops in serum sodium can result in seizures, and acute rises in potassium can result in cardiac dysrhythmias. Glucocorticoid deficiency causes hypoglycemia, fatigue, nausea, and muscle weakness. Significant hypoglycemia can also result in seizures. In severe cases, the patient may develop shock and cardiovascular collapse.6

In this case report, we present an infant who developed adrenal crisis shortly after receiving a high-dose dexmedetomidine infusion. To our knowledge, this incident is only the second case report documenting this potential side effect in the pediatric population and the first of such severity. The use of dexmedetomidine is increasing in pediatric patients. Therefore, it is important to publish this case to increase awareness of this potential side effect.

Case Description

A 49-day-old, ex-term male infant presented to our PICU with respiratory syncytial virus-induced bronchiolitis. The patient had no significant past medical history at the time of admission. After failing heated high-flow nasal cannula and CPAP (continuous positive airway pressure), he was intubated for persistent, severe respiratory distress and hypoxia.
Initially, continuous midazolam and fentanyl were used for sedation and analgesia. He required paralysis with continuous vecuronium shortly after intubation and intermittently as his course progressed.

On the day following intubation, two 2.5 mg (0.4 mg/kg/dose) doses of methylprednisolone were administered due to concern for a reactive airway component. No other steroids were used as his course progressed. He continued to require frequent rescue doses of midazolam and fentanyl for sedation. Adequate sedation was challenging, and he was trialed on continuous propofol, scheduled lorazepam, and scheduled methadone.

On hospital day 11 (mechanical ventilation day 9), he was transitioned to dexmedetomidine in hopes of decreasing narcotic and benzodiazepine cumulative dosing. An initial loading bolus of 3 mcg (0.5 mcg/kg) was administered followed by a continuous maintenance infusion at a rate of 3 mcg/kg/hr. The maintenance infusion rate was decreased to 2 mcg/kg/hr 6 hours later due to hypotension.

Approximately 11 hours after the infusion started, the patient had onset of generalized seizure activity. An electrocardiogram demonstrated right bundle branch block and junctional escape. Serum chemistry at that time showed sodium of 121 mMol/L, potassium of 9.8 mMol/L (nonhemolyzed), bicarbonate of 18 mMol/L, and glucose of 91 mg/dL. Random, nonstimulated serum cortisol at that time was 10 mcg/dL. Electroencephalogram confirmed generalized seizure activity. Dexmedetomidine was discontinued, and stress dose intravenous hydrocortisone was started in addition to antiepileptics and 3% saline. A lumbar puncture was performed, and studies were not indicative of meningitis.

By that afternoon, the patient’s serum sodium had normalized and seizure activity had terminated. Hydrocortisone was slowly tapered and ultimately discontinued over the next 4 days. The patient had a complete recovery and was discharged home on hospital day 29 without any steroids or antiepileptics.

Discussion

Etomidate is a sedative medication that is well known to cause adrenal suppression. The mechanism is direct inhibition of the 11β-hydroxylase enzyme in the adrenal cortex. Etomidate’s imidazole ring structure is responsible for this inhibition.7 The structure of dexmedetomidine is similar to etomidate in that both have an imidazole ring.

As a result, there has been concern that dexmedetomidine could have similar effects on adrenal function. One animal study showed decreased serum cortisol and decreased cortisol response to adrenocorticotropic hormone stimulation following exposure to dexmedetomidine.8 However, studies in humans have largely shown no clinically significant impact on adrenocortical function,5,8,9 likely because dexmedetomidine causes adrenal suppression at concentrations above 10⁻⁶ M while the therapeutic concentration in humans is 10⁻⁹ M.5 There is at least 1 case report of transient adrenal suppression occurring with clinical use in a pediatric patient.4 In that report, dexmedetomidine was administered to a 10 kg pediatric burn patient for 6.5 days with a maximum dose of 2.7 mcg/kg/hr. The patient developed transient adrenal suppression 4 days after the infusion was discontinued. His presenting symptoms were lethargy and hypotension. This use is similar to our maximum dose, but a much longer duration than in our case.

Our patient had a more rapid onset of symptoms with significant electrolyte abnormalities and seizures after a shorter duration of treatment. This timeline correlated directly with the addition of dexmedetomidine only 11 hours earlier and corrected rather rapidly after it was discontinued. His presenting symptoms were lethargy and hypotension. This use is similar to our maximum dose, but a much longer duration than in our case.

It is important to note that the serum cortisol would be expected to be much higher in the setting of this patient’s critical illness. Furthermore, the serum glucose was normal. This finding argues for partial adrenal insufficiency primarily impacting mineralocorticoid production rather than complete insufficiency with concomitant glucocorticoid deficiency. It is possible that continuation of the infusion may have ultimately resulted in complete adrenal insufficiency.

The infusion rate administered to our patient was higher than what is commonly reported in the literature. The initial higher dose of 3 mcg/kg/hr was chosen given the patient’s increased threshold for sedation noted with previous medications. After decreasing to 2 mcg/kg/hr, the dosing was within commonly accepted dosing ranges. The high dose coupled with his critical illness may
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explain the profound impact on adrenocortical function. In follow-up, our patient has not experienced recurrence of his adrenal insufficiency that would suggest an underlying adrenal pathology.

It is plausible that his serum drug concentrations rose above the $10^{-6}$ M level known to result in adrenal suppression. There was no suggestion of hepatic or renal impairment that could have blunted metabolism or clearance of the drug resulting in higher serum concentrations. Our patient had not been treated with high-dose or prolonged courses of steroids and was not receiving any other medications known to cause adrenal suppression. Thus, the most likely etiology for his adrenal crisis is dexmedetomidine.

Conclusion

This case report suggests that, contrary to what is reported in the current literature, the potential exists for considerable adrenocortical impact from high-dose dexmedetomidine. As a result, caution should be exercised when this medication is used at high doses or in patients with possible underlying adrenal pathology.

References


Correspondence

Address to: Jeremy Loberger, MD, Greenville Health System, Internal Medicine/Pediatrics, 701 Grove Rd, Greenville, SC 29605 (jloberger@ghs.org)