



CASE REPORT

Transient Asystole Linked to Dexmedetomidine Infusion

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Abstract

Background: Five adult medical, critically ill patients developed bradycardia leading to asystole while receiving dexmedetomidine infusion.

Materials and methods: This is a case series of five adult patients obtained from the medical intensive care unit in a community teaching hospital between May 2019 through August 2020. These patients were each receiving dexmedetomidine infusion while on invasive mechanical ventilation leading to periods of asystole that resolved after stopping dexmedetomidine infusion in all five patients.

Results: The five patients were mechanically ventilated while receiving dexmedetomidine infusion and experienced periods of brief asystole triggered by vagal stimulation induced by airways suctioning or coughing. Each episode was resolved without intervention. Despite the presence of confounding factors, such as other sedatives and chronotropic medications, it was concluded the main reason for the potentiated vagal response was the presence of dexmedetomidine infusion.

Conclusions: The routine use of continued infusion of dexmedetomidine can lead to asystole if instigated by common vagal stimulation of the trachea during mechanical ventilation.

Keywords

Dexmedetomidine, Asystole, Vaso-vagal

Dexmedetomidine decreases anxiety, and delirium by acting on the locus coeruleus and has the added benefit of having a narcotic sparing effect and furthermore has no respiratory suppression. The most common side effects of dexmedetomidine are hypotension and bradycardia which are dose dependent [1]. Through its sympatholytic mechanism, it exhibits direct AV and SA nodal inhibitory effect and heightened vagal tone via the baroreflex-mediated parasympathetic activation. Dexmedetomidine is highly lipophilic with rapid distribution and elimination ($t_{1/2} = 2-2.5$ hrs). It is eliminated through hepatic metabolism and largely excreted in urine [2]. Per manufacturer (Hospira), bradycardia, defined as HR < 40 or $> 30\%$ reduction from baseline, was reported in 14% of cases [3]. There are scarce reports however in the literature of severe bradycardia including brief asystole episodes, albeit all in association with other factors contributing to asystole and are primarily in the pediatric literature [4-6]. In all our five reported cases, dexmedetomidine was hypothesized to be the culprit behind the potentiated vagal induced asystole events. All five cases were noted to be males ranging from 49 to 67-years-old who had been on mechanical ventilation treated for acute respiratory failure for several days before the asystole events.

Introduction

Dexmedetomidine is a highly selective central alpha 2 receptor agonist with favorable effects when used for sedation in mechanically ventilated patients.

Case Series

Case 1

A 67-year-old male with a history significant for schizophrenia, hepatitis C, hypertension, and



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hyperlipidemia presented to the emergency room on 5/22/19 with garbled speech and twitching after a fall. He was admitted for stroke evaluation. His contrast tomography (CT) brain was negative for acute intracranial abnormality. On day 2 of admission, he developed fever and was started on empiric Vancomycin and Rocephin for possible meningitis. On day 4 of admission, he became tachycardic, tachypneic, and hypoxemic requiring transfer to ICU. His chest X-ray was remarkable for bilateral infiltrates and concern for acute respiratory distress syndrome (ARDS). Due to increased agitation, work of breathing, and tachypnea the patient was intubated and placed on mechanical ventilation later that day. For sedation he was administered a propofol infusion at 15 mcg/kg/min and dexmedetomidine infusion at 0.6 mcg/kg/hr. The patient clinically improved and on day 14 of admission, day 10 of mechanical ventilation, his propofol was discontinued and he underwent a spontaneous breathing trial (SBT) with pressure support (PS) of 5 cmH₂O and CPAP of 5 cmH₂O following a spontaneous awakening trial (SAT). During the SBT, the patient began to cough and instantly his heart rate dropped into the 30's followed by a one-minute period of asystole. A code blue was called but the patient spontaneously returned to sinus rhythm. He was placed back on assist control (AC) ventilator mode. Fifteen minutes later the patient had another episode of vigorous coughing, requiring suctioning, leading to severe bradycardia followed by another one-minute episode of asystole that spontaneously resolved. At this time the patient was given 1 mg IV atropine, dexmedetomidine was discontinued, and his propofol was restarted. On the following day, he continued to have transient mild bradycardia associated with coughing spells but his heart rate would maximally drop to the 40's then recuperate into the 90's-100's within a few seconds. He was able to tolerate suctioning with only a mild decrease in heart rate without further periods of asystole. After these asystole events, his troponin remained at 0.03 and creatinine (SCr) remained at 0.8. While on a dexmedetomidine infusion, the maximum rate received was 0.06 mcg/kg/hr. During these episodes of severe bradycardia or long pauses, he was receiving multiple medications which included nebulized albuterol/ipratropium every 6 hours, clozapine 50 mg in the morning and 400 mg at bedtime, lamotrigine 150 mg twice daily and diazepam 2 mg every 8 hours as needed for agitation. None of these medications are hypothesized to affect the patient's cardiac or respiratory status. QTc was documented to be between 442-462 msec and laboratories including potassium 4.4 mmol/L, magnesium 2.0 mg/dL, SCr 0.7 mg/dL, CrCl > 100 ml/min, ALT 76 IU/L, AST 71 IU/L were within normal limits surrounding these events, demonstrating normal drug metabolism and elimination.

Case 2

A 57-year-old gentleman with a history of chronic

obstructive pulmonary disease (COPD), hyperlipidemia, hypertension, alcohol use, and bilateral carotid stents was admitted on 1/14/2020 for an elective aorto-bilateral profunda bypasses. He underwent a successful surgery on the day of admission without complications. He was kept sedated on mechanical ventilation post-operatively with propofol infusion at 20 mcg/kg/hr and fentanyl infusion 1.5 mcg/kg/hr. On day 2 of hospitalization, dexmedetomidine infusion was added at 0.2 mcg/kg/hr without a bolus in anticipation of extubation. On day 3 of hospitalization, the patient experienced a ten second period of sinus pause while dexmedetomidine was running at 0.9 mcg/kg/hr, the highest rate administered within 24 hours. It was hypothesized that he developed a mucus plug likely causing a vagal response leading to the sinus pause. In addition to dexmedetomidine infusion, the patient received oxazepam 15 mg via NG tube 3 hours prior to the event, IV haloperidol 2.5 mg and IV lorazepam 1 mg given for agitation/anxiety one hour prior to the event in addition to nebulized albuterol/ipratropium every 6 hours. EKG demonstrated sinus tachycardia with nonspecific ST and T wave abnormalities and QTc documented as 490-494 msec. Pertinent laboratories the evening prior and the day of event were all within normal limits and include potassium 4.5 mmol/L, magnesium 2.3 mg/dL, SCr 0.9 mg/dL, CrCl > 100 ml/min, ALT 16 IU/L, and AST 32 IU/L.

Case 3

A 49-year-old male with a history of epilepsy was admitted on 4/14/20 for a one-week history of shortness of breath, fever, and diarrhea. He was found to be in acute hypoxic respiratory failure due to SARS-CoV-2 pneumonia. The patient was intubated on the day of admission and was placed on assist control mode of mechanical ventilation with FIO₂ 100% and PEEP 14. He was placed on a combination of propofol 5 mcg/kg/min and fentanyl 0.5 mcg/kg/day for sedation and analgesia. On day 11 of hospitalization dexmedetomidine infusion was started initially at a rate of 0.2 mcg/kg/hr due to persistent agitation. On day 23 of hospitalization at 06:25, the patient developed a coughing episode while having his oral cavity deeply suctioned without significant desaturation. This was followed immediately with severe sinus bradycardia which progressed to an episode of asystole that lasted ten seconds. The suctioning was discontinued, and his heart rate spontaneously returned to normal without intervention. At this point his dexmedetomidine was running at 1.2 mcg/kg/hr, the maximum rate reached for this patient, and was immediately stopped after the bradycardic event. In the twenty-four hours prior, the patient received the following medications: 3 doses of labetalol 20 mg IV push for HR > 100 at 12:48, 14:23, 17:28, lamotrigine 200 mg, metoprolol tartrate 50 mg, and olanzapine 7.5 mg at 21:00. On the day of the

event, the patient received diazepam 15 mg via NG tube 3 hours prior, fentanyl 25 mcg IV and lorazepam 1 mg IV one hour prior to the event. At the time of the event, hydromorphone 3 mg/hr, midazolam 0.1 mg/kg/hr, and propofol 50 mcg/kg/min were being infused. Pertinent laboratories include: Potassium of 3.9 mmol/L, Magnesium 1.8 mg/dL, SCr 0.8 (CrCl > 100 ml/min), ALT 63 IU/L, AST 41 IU/L. Dexmedetomidine infusion was ultimately felt to be the crucial contributing factor to this patient's transient ventricular asystole as no further episodes occurred in the subsequent hours or days even in the setting of coughing or suctioning despite continuing all other sedatives and medications. The patient ultimately expired three days later secondary to withdrawal of care.

Case 4

A 58-year-old man with a history significant for hepatitis C, hypertension, and hyperlipidemia presented to the emergency department on 5/12/20 with fever, shortness of breath, and fatigue for 2 weeks prior to admission. He tested positive for SARS-CoV-2 and was admitted to the hospital floor. Later on the day of admission, he had increased work of breathing and became hypercapnic requiring emergency intubation by anesthesia service and transfer to the ICU. Dexmedetomidine was started at a rate of 0.2 mcg/kg/hr on day 2 of admission. The patient was unable to be liberated from mechanical ventilation and required a tracheostomy. On day 18, he remained on dexmedetomidine at 0.6 mcg/kg/hr and propofol at 10 mcg/kg/min. While on propofol and dexmedetomidine he was placed on SBT with pressure support (PS) and continuous positive airway pressure (CPAP) and developed sinus bradycardia and an episode of 10 second asystole without associated desaturation below 90%. The patient was then placed back on assist control ventilator mode and his heart rate returned to normal. His propofol infusion was then discontinued but he was kept on dexmedetomidine at a rate of 0.8 mcg/kg/hr. The maximum dexmedetomidine rate within 24 hours of the event was 1 mcg/kg/hr. Within 4 hours of the event, he received 1 dose each of diazepam 10 mg, hydralazine 50 mg and valproic acid 350 mg all via NG tube. Pertinent blood labs prior to the event reflected potassium of 3.6 mmol/L, magnesium 2.2 mg/dL, SCr 1.1 mg/dL (CrCl = 69 ml/min). EKG demonstrated normal sinus rhythm with QTc 439 msec. On day 19 of admission, while on dexmedetomidine, he underwent another SBT which was associated with increased work of breathing and coughing. His heart rate dropped rapidly followed by another 10 seconds period of asystole without associated oxygen desaturation. He was immediately placed back on assist control mode with the return of his heart rate to baseline. Laboratory findings remained within normal limits. The patient received Hydralazine 50 mg, valproic acid 350

mg, fentanyl 50 mcg IV push and labetalol 20 mg IV within 3 hours of this event. Despite these episodes his troponin remained < 0.01. Dexmedetomidine was then discontinued without any similar severe bradycardia or asystole episodes. These episodes were believed to be due to vagal responses associated with severe cough while having an endotracheal tube in place; potentiated by dexmedetomidine infusion.

Case 5

A 63-year-old male with a history of type 2 Diabetes mellitus, COPD, tobacco abuse, hypertension and hyperlipidemia presented to the hospital on 7/12/20 after a witnessed out-of-hospital cardiac arrest. While it was unclear of his initial downtime, EMS arrived, and the patient underwent approximately eight minutes of ACLS protocol. The patient received defibrillation twice and 3 mg of epinephrine in total by EMS before ROSC. The patient was admitted to the intensive care unit and underwent targeted temperature management per hospital protocol. The patient received fentanyl 0.5 mcg/kg/hr and propofol 5 mcg/kg/min for sedation. Amiodarone was also started at 1 mg/min then reduced to 0.5 mg/min and the patient was placed on heparin infusion per protocol to therapeutic PTT. After completing the rewarming protocol on day 4 of admission, dexmedetomidine infusion was started at a rate of 0.2 mcg/kg/hr to help wean the patient off propofol and fentanyl infusions in order to properly perform a neurologic evaluation and exam. Dexmedetomidine infusion rate reached a max rate of 0.5 mcg/kg/hr and subsequently was decreased to a rate of 0.3 mcg/kg/hr. While he was undergoing endotracheal tube suctioning, he became significantly bradycardic and had a 10 second period of asystole. This occurred multiple times with suctioning and each time his rhythm would spontaneously return to normal without intervention. At that point, dexmedetomidine infusion was stopped. The patient received one dose of labetalol 10 mg IV push and nebulized albuterol/ipratropium 4 hours prior to the initial event and was discontinued once the initial adverse event occurred. Prior to the event, EKG demonstrated normal sinus rhythm with low voltage QRS and QTc of 472. All laboratories were within normal limits including troponin which did not change after the event. The patient experienced no further transient episodes of asystole after his dexmedetomidine infusion was stopped. Unfortunately, due to the patient's evolving cerebral edema and wave suppression on EEG, the patient's code status was changed to comfort care, and he was terminally extubated two days after the event.

Conclusion

Each of these cases were associated with a period of asystole following either endotracheal tube suctioning or vigorous coughing with ETT or tracheostomy

tube in place while on a dexmedetomidine infusion. We hypothesize that the episodes of asystole were accentuated vagal events directly predisposed by the effect of dexmedetomidine.

As far as we know, this is the first case series in the medical literature that describes potentially lethal asystole events caused by the routine use of dexmedetomidine infusion in mechanically ventilated adult patients with acute respiratory failure. In the case series we described, we found that increased vagal tone associated with stimulation of tracheal mucosa, induced by either tracheal suctioning or vigorous coughing attacks can trigger transient asystole in intubated or tracheostomy tube patients who are on dexmedetomidine infusion. In all our reported cases, the episodes of asystole ceased to exist quickly after discontinuing dexmedetomidine despite resuming the same tracheal stimulation. This likely excludes the possibility that the patients had intrinsic predisposition to bradycardia.

Bradycardia in intubated, mechanically ventilated patients is not uncommon and is typically multifactorial from medication effects, preexisting myocardial conduction defects, myocardial ischemia, and metabolic or endocrine abnormalities. Bradycardia associated with endotracheal tube suctioning is not an infrequent occurrence in the PICU, especially in infants and neonates. Asystole resulting from progressive bradycardia during endotracheal suctioning, however, is an extremely rare event especially in older children and adolescents [7,8]. In adults, tracheal suctioning is not uncommonly associated with trivial bradycardia. Severe bradycardia or asystole was described in association with vigorous and prolonged stimulation of larynx or trachea such as during suspension microlaryngoscopy and tracheal dilatation [9,10]. C3-5 spinal cord complete transection injury is associated with unopposed vagal responses due to absent sympathetic activity. In a case series, 4 newly tetraplegic adults due to recent complete C3-5 transection spinal cord injury developed short lived bradycardia or asystole following tracheal suctioning associated with desaturation [11].

Very scarce cases of asystole were reported in mechanically ventilated adults while receiving dexmedetomidine, albeit, these cases were confounded with remarkable factors known to induce vagal stimulation or bradycardia. In a case report, a 52-year-old female with myasthenia gravis developed asystole during sternal retraction for thymectomy following anesthesia induction with dexmedetomidine along with fentanyl, midazolam and isoflurane after being prepared preoperatively with pyridostigmine [6]. Both traction sternotomy and pyridostigmine can induce significant parasympathomimetic activation.

Of note, 3 out of 5 patients in our case series were on other medications that could potentially enhance

the bradycardic effect including propofol, beta blockers, and narcotics in the form of either fentanyl infusion, boluses or hydromorphone infusion. Some will argue that the coadministration of certain medications facilitated the accentuated vagal events. In the case of beta blockers, which were co-administered in two cases a few hours before the events, the rapid resolution of bradycardic response to vagal stimuli after stopping dexmedetomidine infusion reflects the shorter elimination half-life of dexmedetomidine. The baseline heart rate in these cases of medication co-administration was normal to borderline tachycardic before vagal stimulation. The mechanism of action of beta blockers is not primarily vagal as well. This all argues against the significant contribution of beta blockade in the two co-administration case scenarios. Overdose with narcotics or benzodiazepines can be associated with bradycardia and hypotension although the exact mechanism of bradycardia is not clear. The doses of narcotics or benzodiazepines were not above average and in most of our reported cases they had been administered for days before dexmedetomidine was started without any observed bradycardia or exaggerated vagal responses. In our cases, these medications were continued as the main sedation and analgesia regimen post events without subsequent return of serious bradycardia. Dexmedetomidine was administered at a dose of 0.02 mcg/kg/hr followed by continuous infusion rate increased by 0.01 mcg/kg/hr every 30-60 minutes to SAS of 4 or maximum of 1.5 mcg/kg/hr. Evidence suggests that if the dexmedetomidine plasma concentration exceeds 1.2 ng/ml, it induces a decrease in cardiac function. However, Takada, et al. concluded that cardiac arrest is not usually correlated with plasma concentrations of dexmedetomidine [4]. In our five cases, the infusion was running between 0.5 mcg/kg/hr to 1.2 mcg/kg/hr during the asystole events. This suggests that the maximum infusion rate of dexmedetomidine does not influence if a cardiac event will occur. In one of the cases, lowering the dose of dexmedetomidine attenuated bradycardic effect associated with vagal stimulation.

Dexmedetomidine is commonly used as a multimodal ICU sedation medication and is typically favored over benzodiazepines because of the lower risk of extended sedation or respiratory depression; in addition to its utility during SBT. Our case series, however, indicates that the routine use of dexmedetomidine can be associated with serious bradycardic events.

We recommend monitoring closely the patients on invasive mechanical ventilation via ETT or tracheostomy tube while on dexmedetomidine infusion, particularly if they are on other medications that can predispose to bradycardia and stop the infusion or lower the dose significantly to a much safer level at the earlier signs of accentuated vagal responses.

Authors Declarations

We have no conflicts of interest to disclose.

There are no relevant financial disclosures to make.

All authors equally contributed to this manuscript.

References

1. Gertler R, Brown HC, Mitchell DH, Silvius EN (2001) Dexmedetomidine: A novel sedative-analgesic agent. *Proc (Bayl Univ Med Cent)* 14: 13-21.
2. Karol MD, Maxe M (2000) Pharmacokinetics and interaction pharmacodynamics of dexmedetomidine in humans. *Best Practice & Research Clinical Anaesthesiology* 14: 261-269.
3. Hoy SM, Keating GM (2011) Dexmedetomidine. *Drugs* 71: 1481-1501.
4. Takata K, Adachi YU, Suzuki K, Obata Y, Sato S, et al. (2014) Dexmedetomidine-induced atrioventricular block followed by cardiac arrest during atrial pacing: A case report and review of the literature. *J Anesth* 28: 116-120.
5. Terlach T, Murphy CV (2009) Dexmedetomidine-associated bradycardia progressing to pulseless electrical activity: Case report and review of the literature. *Pharmacotherapy* 29: 1492.
6. Ingersoll-Weng E, Manecke GR, Thistlethwaite PA (2004) Dexmedetomidine and cardiac arrest. *Anesthesiology* 100: 738-739.
7. Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colino MD (2000) The effects of increasing plasma concentrations of dexmedetomidine in humans. *Anesthesiology* 93: 382-394.
8. Shea PL, Conner JM, Bhaktan RT, Spaeder MC (2014) Recurrent asystolic episodes associated with endotracheal suctioning: Role of nebulized atropine sulfate.
9. Redman AJ, White GD, Makkad B, Howell R (2016) Asystole from direct laryngoscopy: A case report and literature review. *Anesth Prog* 63: 197-200.
10. Sutura PT, Smith CE (1994) Asystole during direct laryngoscopy and tracheal intubation. *J Cardiothoracic Vasc Anesth* 8: 78-80.
11. Mathias J (1976) Bradycardia and cardiac arrest during tracheal suction Mechanisms in tetraplegic patients. *Eur J Intensive Care Med* 2: 147-156.