Case Report

Significant Bradycardia in Critically Ill Patients Receiving Dexmedetomidine and Fentanyl

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Purpose

To report a case series of three patients who developed significant bradycardia while receiving the combination of dexmedetomidine and fentanyl for sedation and analgesia. Materials and Methods. This is a case series of patients obtained from a mixed medical, surgical, and cardiac ICU in a community teaching hospital. Three intubated patients receiving fentanyl and dexmedetomidine infusion developed sudden bradycardia requiring intervention. In all three cases, adjustments to therapy were required. Results. All three patients experienced significant bradycardia, with a heart rate less than 50 bpm, and one patient briefly developed asystole. In Case 1, the fentanyl infusion rate was reduced by 67% and the dexmedetomidine infusion rate was reduced by 25%. In Case 2, the sedation was changed to midazolam, and in Case 3, both fentanyl and dexmedetomidine were discontinued. In all three cases, there were no further incidences of significant bradycardia following intervention. Conclusions. Fentanyl used in combination with dexmedetomidine can result in clinically significant bradycardia. Further study is warranted to identify risk factors and elucidate the mechanisms that result in life-threatening bradycardia.

1. Introduction

The current pain, agitation, and delirium guidelines encourage the use of fentanyl with sedation strategies using nonbenzodiazepine sedatives [1]. Dexmedetomidine is an effective sedative that is often used in conjunction with opioids such as fentanyl in the critical care and anesthesia setting. Bradycardia and hypotension are well-known associations with dexmedetomidine, yet no human studies have examined the occurrence of drug-induced bradycardia secondary to the combination of dexmedetomidine and fentanyl. One study demonstrated attenuation of the tachycardia response to flexible bronchoscopy with the combination of dexmedetomidine-fentanyl compared to propofol-fentanyl [2]. Here we report three cases in which a synergistic interaction between fentanyl and dexmedetomidine may have contributed to clinically relevant bradycardia.

2. Case Series

2.1. Case 1. Patient was a 59-year-old male with a past medical history of cirrhosis, ulcerative colitis, esophageal varices with previous banding, hypertension, and hyperlipidemia. He had advanced alcoholic cirrhosis, with a Model for End-Stage Liver Disease (MELD) score of 17, and was admitted with a large right pleural effusion secondary to ascites. His initial pharmacologic management included furosemide, spironolactone, albumin, midodrine, pantoprazole, lactulose, rifaximin, and antibiotics for a possible pneumonia. During his admission, he received nadolol for portal hypertension, with his heart rate averaging between 55 and 85 bpm, but this was discontinued on hospital day four.

Despite multiple thoracenteses, he ultimately required intubation on hospital day six secondary to worsening respiratory failure. His weight and select values at this time are
was switched to dexmedetomidine alone due to hypotension. Throughout his ICU course, he required continuous renal replacement therapy and total parenteral nutrition. An echocardiogram from two months prior demonstrated an ejection fraction of 50% and normal diastolic function. Dexmedetomidine was titrated up to 0.7 mcg/kg/hour to achieve a goal RASS of −2 with no hemodynamic complications.

After two days of dexmedetomidine therapy, an intravenous bolus dose of fentanyl 50 mcg was given for acute pain, followed by an intravenous bolus dose of metoclopramide 5 mg given 30 minutes later. Within one hour, the patient’s heart rate rapidly decreased, leading to a six-second asystolic pause. The pulse spontaneously returned, but the heart rate remained between 30 and 35 bpm for 15 minutes. Dexmedetomidine infusion was immediately discontinued, and the heart rate ultimately improved to normal without intervention. The patient was switched to midazolam infusion, and there were no further episodes. During the time of the asystole, the patient was also receiving rifaximin for a resolving hyperammonemia, famotidine, heparin, cefazolin, insulin, methimazole, metoclopramide, and norepinephrine. Select labs at this time are provided in Table 1. The patient ultimately expired on hospital day 21 due to cardiac arrest following a prolonged course.

### Table 1: Select demographic data and labs at time of bradycardia.

| Case 1 | Case 2 | Case 3 |
|--------|--------|--------|
| Weight (kg) | 77 | 86.8 | 93.4 |
| Body mass index (BMI) | 29.3 | 25.1 | 29.9 |
| Serum creatinine (mg/dL) | 1.10 | 1.78 | 0.61 |
| Serum CO\(_2\) (mEq/L) | 28 | 20 | 27 |
| Blood urea nitrogen (mg/dL) | 28 | 41 | 24 |
| Albumin (g/dL) | 1.9 | 2.6 | 4.1 |
| Protein (g/dL) | 5.4 | 5.3 | 4.6 |
| ALT (units/L) | 7 | 4 | 48 |
| AST (units/L) | 29 | 37 | 46 |
| Alkaline phosphatase (units/L) | 60 | 164 | 74 |
| INR | 2.12 | 1.14 | 1.03 |
| aPTT (seconds) | 37.3 | 24.1 | 30.6 |

ALT: alanine aminotransferase; AST: aspartate aminotransferase; INR: international normalized ratio; aPTT: activated partial thromboplastin time.
Dexametomidine is an \(\alpha_2\) adrenergic receptor agonist, with studies demonstrating a high ratio of \(\alpha_2/\alpha_1\)-activity (1620:1) [3]. It is selective for G protein-binding adrenergic receptors, including \(\alpha_{2A^{-}}, \alpha_{2B^{-}}, \alpha_{2C^{-}}\) adrenoceptor subtypes. \(\alpha_{2A^{-}}\) Adrenergic receptor agonism provides sedative and antinociceptive properties, while \(\alpha_{2B^{-}}\)-adrenergic receptor has vasoconstrictive properties. \(\alpha_{2C^{-}}\) Adrenoceptor agonism has a variety of effects such as regulating dopaminergic and behavioral responses [4]. The presence of \(\alpha_2\) adrenergic receptors in the presynaptic and postsynaptic terminals contributes to its sedative and analgesic properties. The activation of the presynaptic terminal leads to decreased transmission of pain signals, and activation of the postsynaptic terminal inhibits the sympathetic nervous system, elucidating its hypotensive and bradycardic effects [5]. The activation of \(\alpha\) adrenergic receptors causes hyperpolarization of membranes from potassium channel activation, which decreases norepinephrine release. This is significant in the locus coeruleus, which provides adrenergic innervation to the brain and associated with brain functions such as arousal and sleep [4].

Data regarding the association between dose of dexametomidine and the incidence of bradycardia seem inconclusive. One retrospective study that compared low- and high-dose dexametomidine in ICU patients showed no significant difference in the incidence of hypotension and bradycardia [6]. Another study that measured plasma concentrations of dexametomidine demonstrated an indirect relationship between concentration and heart rate [7]. Lastly, a retrospective cohort study identified risk factors such as advanced age and low baseline arterial blood pressure to be associated with hemodynamic instability with dexmedetomidine but did not identify doses greater than 0.7 mcg/kg/hour to be an independent risk factor [8]. Interestingly, cardiac or sedative medications given concurrently with dexametomidine were also not associated with higher rates of instability [8].

Fentanyl exerts its effects by binding to opioid receptors in the brain and spinal cord [9]. Fentanyl is known for its relatively favorable hemodynamic profile, especially in the critically ill when cardiovascular depression is undesired [10]. Although uncommon, fentanyl-induced bradycardia is known adverse effect, yet the exact mechanism is unknown. A proposed mechanism involves the indirect increase of parasympathetic activity in the cardiac vagal neurons in the nucleus ambiguus. The stimulation of \(\mu\)-opioid receptors in rats by endomorphin-1 postsynaptically via the G protein pathway inhibits calcium currents, leading to increased vagal stimulation to the heart [11]. In addition, fentanyl specifically has been suggested to have an inhibitory role in GABAergic neurotransmission in cardiac vagal neurons, thus increasing parasympathetic activity with induced bradycardia [12].

This case series highlights three critically ill patients who developed significant bradycardia while receiving the combination of dexametomidine and fentanyl for sedation and analgesia. According to the Drug Interaction Probability Scale (DIPS), all three cases can be classified as probable drug interactions [13]. Although these drugs individually exert their effects via different pathways, little is known regarding a synergistic or additive effect on heart rate reduction. In 1994, Salmenperä and colleagues postulated that fentanyl may augment the bradycardic effects of dexametomidine in a dog model [14]. A shared pathway of \(\mu\)-opioid and \(\alpha_2\) adrenergic receptors is the stimulation of the guanine nucleotide regulatory protein, leading to the decreased levels of adenylate cyclase. The downstream effects include hyperpolarization of the membranes secondary to the efflux of potassium ions [14, 15]. This may explain the additive or synergistic effects of bradycardia.

To our knowledge, this is the first such case series reporting clinically significant bradycardia among humans that appeared to be worsened when fentanyl and dexmedetomidine were given concomitantly. This finding is contradictory to previous reports that concomitant use of sedatives with dexametomidine does not increase the risk of hemodynamic instability [8]. Our findings warrant several considerations for the ICU clinician. First, as dexametomidine use in critically ill patients continues to expand, clinicians should be aware that significant bradycardia can develop when dexametomidine is used in combination with fentanyl, a commonly used analgesic in the ICU. This effect may be exaggerated in patients with liver dysfunction, as both medications are metabolized primarily via the liver. This effect may also be more pronounced in patients receiving prolonged infusions of dexametomidine. Although the Food and Drug Administration suggests that continuous infusions of dexametomidine should not exceed 24 hours [16], current practice often requires extension of the infusion duration beyond this recommendation. Indeed, for all three cases reported here, significant bradycardia or asystole occurred after dexametomidine was used for greater than 24 hours. Lastly, patients receiving fentanyl and dexametomidine may also be at an increased risk if they receive other agents that can cause bradycardia, including propofol and metoclopramide, both of which are frequently used in the ICU. Further research is warranted to identify risk factors and elucidate the mechanisms that result in life-threatening bradycardia.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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