CLINICAL VIGNETTE

Bradyarrhythmia after Fentanyl Overdose with Recurrence Following Buprenorphine for Opioid Withdrawal

Nico Conti, MD and Veronica Ramirez, MD

Introduction

Fentanyl, a synthetic opiate, continues to be a leading cause of opioid-related morbidity and mortality. In 2021, more than 6,800 people died due to synthetic opioid-related drug overdose in California, and over 5,700 of these deaths were associated with fentanyl.[1] Fentanyl can cause several cardiovascular abnormalities, including arrhythmias, cardiomyopathy, and even acute coronary syndrome.[2] We present a case of new-onset bradyarrhythmia that developed 48 hours after fentanyl overdose which followed buprenorphine administration.

Case Presentation

A 49-year-old male with history significant for opioid use disorder, on buprenorphine, was brought to the emergency department by ambulance after being found down. Emergency medical services noted the patient to have pinpoint pupils and decreased respiratory drive. He was given intranasal naloxone with improvement in his mental status and respiratory rate. The patient was then transported to the emergency department for further evaluation. Prior medical history includes remote spinal infection complicated by chronic BLE spasticity and numbness. He is wheelchair dependent and has a chronic indwelling Foley catheter,

The patient acknowledged using fentanyl the morning of admission, and he reported being treated for fentanyl overdose multiple times in the past. He took buprenorphine at home and he last used this medication three days prior to admission. He denied any fevers, chills, nausea, vomiting, shortness of breath, or chest pain. He did report several days of pelvic discomfort and had not had his Foley catheter exchanged in quite some time.

In the ED, his initial vitals were notable for temperature 36.2 degrees Celsius, heart rate 110 beats per minute, blood pressure 159/110 mmHg, respiratory rate 23 breaths/min, and oxygen saturation of 82% on ambient air. He was placed on 15L non-rebreather mask with improvement to 100%, and eventually weaned to 3L supplemental oxygen. His exam was notable for multiple superficial facial abrasions, clear to auscultation of the lungs throughout, regular rate and rhythm on cardiovascular exam, decreased sensation to light touch in bilateral lower extremities (which was chronic from his prior spinal infection), and a Foley catheter with dark yellow urine in the bag without hematuria or clots. His laboratory results were notable for a urine toxicology screen positive for fentanyl, buprenorphine, cannabinoids, and benzodiazepines. Urinalysis was positive for nitrites and leukocyte esterase. Chest x-ray revealed right greater than left bibasilar atelectasis. Given concern that the patient may have aspirated when somnolent from the fentanyl overdose episode and fall, he was started on intravenous ceftriaxone and metronidazole for aspiration pneumonia coverage. The antibiotics also covered possible catheter-associated urinary tract infection, after his Foley catheter was exchanged. Given the hypoxia, the patient was admitted to the hospitalist service for further management.

On hospital day two, the patient reported severe body aches and cramps. He felt he was starting to go into withdrawal from fentanyl. He was initiated on buprenorphine 8mg every eight hours with non-opiate adjunct medications to help with associated symptoms. These included gabapentin, acetaminophen, and baclofen. The patient reported minimal improvement in his body aches. He was weaned off supplemental oxygen. On hospital day three, telemetry monitoring noted new bradycardia, with heart rate 40's-50's beats per minute. The patient denied any palpitations, chest pain, dizziness, or lightheadedness. Twelve-lead electrocardiogram showed sinus rhythm with heart rate 67 and no evidence of heart block. QTc resulted as 458. Given concern that the new bradycardia may be related to recent re-initiation of buprenorphine, the dose was decreased to 8mg every 12 hours, and baclofen was stopped given possible interaction. However, on hospital day four, telemetry monitoring continued to show resting heart rate in the 30's-40's beats per minute, though he remained asymptomatic. Transthoracic electrocardiogram did not reveal any structural abnormalities. Electrophysiology was consulted. The patient remained asymptomatic, without EKG evidence of high-grade block, there was no indication for permanent pacemaker placement. They believed his bradyarrhythmia was likely related to the patient's recent fentanyl overdose, and recommended continued supportive care. The patient's heart rate gradually improved and he tolerated titration of buprenorphine back to his home dose of 16mg twice daily which had been confirmed with the CURES report, with no recurrence of sinus bradycardia. His body aches also improved, and he was transitioned to oral antibiotics to

complete a total of seven days of treatment for both aspiration pneumonia and catheter-associated urinary tract infection. The patient also suffered from housing insecurity, and he was discharged to recuperative care as well as a program for medication-assisted treatment of opioid use disorder.

Discussion

Globally, opioid use disorder is a pandemic, evidenced by the frequency of its abuse. The World Health Organization estimates 27 million persons have opioid use disorder and require treatment. It also carries a high mortality rate, estimated to be 15-20 times higher than those not suffering from opioid use disorder.[3] Fentanyl is a frequently abused opioid, and substantial data has documented the burden of fentanyl-related mortalities from the earliest reports in the 1970-1980s through present day due to its deleterious effects, one of these being hemodynamic changes.

Bradycardia following the administration of fentanyl, such as use for anesthesia, is an effect of the drug which has been well-documented. This had been demonstrated decades ago in studies which examined the effect of anesthesia on dogs.[4] Further still, surgical studies from 2002 and 2007 observed bradycardia in human patients undergoing anesthesia with rates of 16.6-18% respectively in those receiving fentanyl.[5] There are also case reports detailing prescribed transdermal fentanyl patches resulting in bradycardia, as well as transdermal fentanyl misuse (such as oral ingestion) resulting in bradycardia amongst other deleterious opioid effects.[5,6] This demonstrates the risk of bradycardia even with commonly prescribed fentanyl formulations.

The mechanism of fentanyl induced bradycardia is believed to be from activation of μ-opioid receptors increasing parasympathetic tone via the nucleus ambiguus of cardiac vagal neurons. These effects are likely exerted by G-protein pathway inhibition of calcium channels. In addition, fentanyl is postulated to have a GABA inhibitory role in cardiac vagal neurons, further enhancing cardiac parasympathetic activity. Overall, this increases vagal stimulation of the heart.[7]

Treatment of opioid use disorder is primarily through pharmacotherapy, with drugs such as buprenorphine. This is a high affinity, partial μ-opioid agonist. Buprenorphine reduces opioid use, cravings and opioid withdrawal symptoms. In addition it blocks effects of exogenously used opioids that may cause other adverse effects including respiratory depression. Compared to full opioid agonists, buprenorphine has a better safety profile and lower likelihood of abuse, and allows for daily or less than daily dosing given its long half-life.[3,8]

Buprenoprhine administration, however, has also been observed to have the adverse effect of bradycardia. Bradycardia has been reported in post-operative lower-limb surgery patients receiving buprenorphine as intrathecal analgesia.[9]

This patient had sinus bradycardia noted several days after hospital admission for fentanyl overdose, with onset after buprenorphine initiation, during opioid withdrawal. It is possible a combined effect of recent illicit fentanyl use, in addition to starting treatment with buprenorphine, resulted in this patient's bradycardia as both fentanyl and buprenorphine increase the risk of bradycardia. Alternatively, it is possible that this patient's bradycardia was from buprenorphine initiation alone. Given the pharmacokinetics of buprenorphine, the patient may have experienced a "ceiling effect" of buprenorphine, without other common opioid side effects such as respiratory depression. This may have confused the etiology of his bradycardia. The patient's bradycardia persisting after temporarily stopping buprenorphine may be explained by its lengthy half-life and high affinity for the μ-opioid receptor. It is possible his illicit fentanyl use had a role in the bradycardia because when this patient started buprenorphine the second time, bradycardia did not recur, likely because all the illicit fentanyl the patient used had finally been metabolized.

A strikingly similar case report exists in which an elderly patient experienced significant bradycardia and hypotension requiring hospital admission after sublingual induction of buprenorphine. The patient was in opioid withdrawal when the buprenorphine was started and bradycardia with hemodynamic stability occurred afterward, similar to the patient reported here. Furthermore, that patient's withdrawal symptoms were secondary to their prescribed fentanyl patches.[10]

Conclusion

This case highlights the impressive prevalence of opioid use disorder and fentanyl use, both illicitly and prescribed, and the possibility of it resulting in bradycardia. It also reflects on the possibility of adverse effects of a common pharmacologic treatment of opioid use disorder – buprenorphine. This case suggests that recent fentanyl use coupled with buprenorphine initiation during opioid withdrawal may have an additive effect on reducing the heart rate of a patient. While bradycardia is a known adverse effect of opioids such as fentanyl and buprenorphine, in current medical practice it is often thought to be a rare complication. Given the prevalence of opioid abuse and how commonly prescribed both fentanyl and buprenorphine are, providers should keep in mind this adverse effect when initiating these drugs. Providers should also identify patients who need closer monitoring on these agents, such as patients with low resting heart rate and low baseline blood pressure. In addition, given that initiating buprenorphine during opioid withdrawal is a common clinical scenario, further studies investigating patient risk factors associated with fentanyl or buprenorphine-induced bradycardia may help further identify those at risk for bradycardia in these situations.

REFERENCES

1. California Department of Public Health. Fentanyl and Overdose Prevention. [Internet] Available at:

https://www.cdph.ca.gov/Programs/OPA/Pages/Communications-Toolkits/Fentanyl-Overdose-Prevention.aspx.

2. **Badar F, Ashraf A, Bhuiyan MR, Bimal T, Iftikhar A**. A Peculiar Case of Fentanyl-Induced Cardiomyopathy. *Cureus*. 2022 Aug 5;14(8):e27708. doi: 10.7759/cureus.27708. PMID: 36081981; PMCID: PMC9440989.
3. **De Aquino JP, Parida S, Sofuoglu M**. The Pharmacology of Buprenorphine Microinduction for Opioid Use Disorder. *Clin Drug Investig*. 2021 May;41(5):425-436. doi: 10.1007/s40261-021-01032-7. Epub 2021 Apr 5. PMID: 33818748; PMCID: PMC8020374.
4. **Arndt JO, Mikat M, Parasher C**. Fentanyl's analgesic, respiratory, and cardiovascular actions in relation to dose and plasma concentration in unanesthetized dogs. *Anesthesiology*. 1984 Oct;61(4):355-61. doi: 10.1097/00000542-198410000-00001. PMID: 6091503.
5. **Hawley P**. Case report of severe bradycardia due to transdermal fentanyl. *Palliat Med*. 2013 Sep;27(8):793-5. doi: 10.1177/0269216312472383. Epub 2013 Jan 22. PMID: 23341102.
6. **Faust AC, Terpolilli R, Hughes DW**. Management of an oral ingestion of transdermal fentanyl patches: a case report and literature review. *Case Rep Med*. 2011;2011:495938. doi: 10.1155/2011/495938. Epub 2011 May 12. PMID: 21629807; PMCID: PMC3099212.
7. **Hui C, Cardinale M, Yegneswaran B**. Significant Bradycardia in Critically Ill Patients Receiving Dexmedetomidine and Fentanyl. *Case Rep Crit Care*. 2017;2017:4504207. doi: 10.1155/2017/4504207. Epub 2017 Sep 6. PMID: 29038737; PMCID: PMC5606045.
8. **Coe MA, Lofwall MR, Walsh SL**. Buprenorphine Pharmacology Review: Update on Transmucosal and Long-acting Formulations. *J Addict Med*. 2019 Mar/Apr;13(2):93-103. doi: 10.1097/ADM.0000000000000457. PMID: 30531584; PMCID: PMC7442141.
9. **Rosenfeldt FL, Houston B, Thompson D, Naqui N, Malcolm AD, Williams BT, Coltart DJ**. Haemodynamic effects of buprenorphine after heart surgery. *Br Med J*. 1978 Dec 9;2(6152):1602-3. doi: 10.1136/bmj.2.6152.1602. PMID: 728741; PMCID: PMC1608864.
10. **Chaparro A, Ravishankar DA, Sethi R**. Should Buprenorphine Induction Dosing Be Lower for the Elderly Population With Opioid Use Disorder? A Case of Buprenorphine-Induced Hemodynamic Instability. *Prim Care Companion CNS Disord*. 2020 Sep 10;22(5):19l02514. doi: 10.4088/PCC.19l02514. PMID: 32910846.