Should Buprenorphine Induction Dosing Be Lower for the Elderly Population With Opioid Use Disorder?

A Case of Buprenorphine-Induced Hemodynamic Instability

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Opioid use disorder (OUD) is increasingly becoming a problem among the elderly population in the United States. The number of Americans aged ≥ 50 years with OUD is projected to double from 2.8 million in 2002–2006 to 5.0 million in 2020.[1] OUD in the elderly is a major concern and an important challenge for physicians due to the rising numbers, higher incidence of pain problems in this population, and increased susceptibility to adverse effects of medications.[2] Buprenorphine acts centrally as a partial μ agonist and κ and delta opioid receptor antagonist.[3–5] Buprenorphine has high affinity for the μ receptor, long duration of action, and a slow dissociation rate.[6] Here, we discuss the case of a elderly man who developed hypotension, bradycardia, and possible respiratory depression following buprenorphine induction.

Case Report

A 73-year-old male nonsmoker with a 10-year history of chronic foot pain, coronary artery disease, hypertension, and arthritis of the left hip and knee was being followed by the pain clinic for the last 10 years. For his pain, he was prescribed hydrocodone 5 mg, which was subsequently increased to 7.5 mg and later to 10 mg up to 4 times a day. Fentanyl was added at 25 mcg and increased to 37 mcg and subsequently to 50 mcg. Over the years, he started to develop criteria for OUD including unsuccessful efforts to cut down on use of the medication, failure to fulfill role obligations at work, and use of the medication in physically hazardous situations. The patient asked to be slowly tapered off the medication by the pain clinic. He was on a fentanyl 12-mcg patch that he used every 3 days and hydrocodone 10 mg 1–2 times a day when he was seen for medication-assisted treatment, as he could not taper further without withdrawal symptoms. He was asked to stop using the fentanyl and hydrocodone and was to be induced on buprenorphine for cravings and withdrawal. At the initial visit, he was on the third day of his fentanyl patch, which he discontinued that night along with the hydrocodone. He was provided a script for ondansetron 4 mg every 8 hours as needed, clonidine 0.1 mg 3 times a day, and hydroxyzine 25 mg twice daily as needed for withdrawal symptoms until he was seen in the clinic. On the day of the buprenorphine induction, the Clinical Opiate Withdrawal Scale[7] was administered, and he scored an 8, which indicated mild withdrawal. He reported withdrawal symptoms of anxiety, pain, restless legs, and insomnia. In the clinic, he was initiated on buprenorphine monotherapy at 2 mg sublingually. After the first dose, he reported improvement in withdrawal symptoms, including pain, anxiety, and restlessness, and no precipitated withdrawal was observed. After 2 hours, he was given a second 2-mg dose. He tolerated that dose as well and reported further improvement in symptoms of anxiety and restlessness but did describe feeling dizzy and fatigued. His vital signs preadministration of the second dose of buprenorphine at 10:15 AM were blood pressure (BP) of 113/62 mm Hg and pulse of 60 bpm. After administration of buprenorphine at 11:30 AM, his BP was 90/50 mm Hg and pulse was 54 bpm; at 11: 45 AM, his BP was 77/52 mm Hg and pulse was 54 bpm. A rapid response team was called and when they arrived found the patient to be lethargic and having difficulty keeping his eyes open. He was taken to the emergency department (ED) for further management.

Upon transfer to the ED, the patient was started on intravenous (IV) naloxone 0.04 mg for lethargy and hypotension with the presumptive diagnosis of buprenorphine toxicity/hypersensitivity. He displayed respiratory depression at 10 breaths/minute. In the ED, the basic laboratory tests were conducted and were unremarkable. His electrocardiogram was within normal limits, venous blood gas was 51, and troponin was negative. He was somnolent and lethargic, and when given naloxone, he became stable hemodynamically. He was subsequently placed on a naloxone IV, and his hemodynamic status continued to improve. He was transferred to the intensive care unit where the naloxone IV 0.04 mg was continued. Overnight, the patient remained hemodynamically stable, and the naloxone IV was stopped the next morning. He was monitored for any change in vitals for 5 hours as suggested by poison control. The patient was deemed stable for discharge 5 hours after stopping the naloxone drip with orders to follow up with the addiction clinic the next day. He was seen the following day to restart medication-assisted

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Prim Care Companion CNS Disord 2020;22(5):19l02514

To cite: 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;22(5):19l02514.

To share: https://doi.org/10.4088/PCC.19l02514

treatment; however, he reported no cravings, withdrawal symptoms, or pain symptoms and decided he did not want to be rechallenged on buprenorphine or try other medication-assisted treatment. The patient was seen a month later and denied any cravings or withdrawal symptoms and reported minimal pain.

Discussion

Buprenorphine is a semisynthetic mixed opiate agonist-antagonist, working as a partial agonist at μ receptors, an antagonist at κ-opioid receptors, and an agonist at delta opioid receptors.[6] Buprenorphine has a partial μ receptor agonism activity, making the danger of overdose, abuse, and toxicity lower compared to full μ agonists.[4] Buprenorphine has a ceiling effect and hence does not typically cause respiratory depression in an overdose.[5] It also dissociates very slowly from μ receptors, which allows for a long duration of action (half-life of 37 hours) and low level of physical dependence.[8] Currently, there are no recommended dosage adjustments based on age alone when starting buprenorphine for OUD.[9] We report a case of hypotension and bradycardia with possible respiratory depression in a 73-year-old man induced on buprenorphine 4 mg the first day of treatment, who tolerated opiates with no complications in the past. The current induction dosing recommendations for sublingual buprenorphine are up to 8 mg the first day, up to 16 mg or higher the second day, and up to 24 mg the third day.[9] Pharmacokinetics are similar between younger adults and the elderly, but younger patients have shown a trend of higher plasma concentrations with transdermal buprenorphine.[10] There is a lack of literature assessing the difference between dosing and pharmacokinetics among the elderly with the use of the sublingual administration form of buprenorphine.

A study[10] comparing use of the transdermal patch among the young and the elderly showed no change in pharmacokinetics among the 2 groups. However, caution has been advised for the use of buprenorphine in patients who are more likely to have comorbidities that may affect buprenorphine metabolism or pharmacokinetics (eg, liver failure patients).[11] There have been case reports of opioid-naive elderly patients who experienced respiratory or neurologic depression due to buprenorphine administration.[12] In 4 of 5 of these cases, high doses of naloxone were needed to treat the respiratory depression associated with buprenorphine use.[12] There are reports[13] in the literature of the hemodynamic effects of buprenorphine after heart surgery, with buprenorphine leading to significant bradycardia due to a direct action of the drug or an indirect action in relieving tachycardia caused by pain and anxiety. Our patient did have a history of coronary artery disease, and administration of buprenorphine might have contributed to the bradycardia.

According to some reports,[14,15] buprenorphine can cause central nervous system and respiratory depression in a dose-dependent manner. With an increase in the dose, a plateau is reached and respiratory depression is not seen when compared to other opiates.[14,15] The ceiling effect is seen more in chronic opioid users than in those who are opioid naive.[14] This observation may explain the course of our patient, who developed central nervous system and respiratory depression at a low dose of 4 mg but was not protected from the ceiling effect of the drug as the dose administered was minimal to the patient though he was not opioid naive.

In an animal study, IV-administered buprenorphine caused a significant depression of arterial pressure and heart rate, but the reduction in heart rate was greater than that in arterial pressure.[16] This finding would also provide the best explanation of unexpected clinical phenomena of buprenorphine in the elderly population as well.

More research is needed to determine if there should be a reduction in induction (first day) dose in elderly patients because of the possibility of bradycardia and respiratory depression with no ceiling effect at a low dose as discussed here. Buprenorphine in the elderly should be used cautiously by clinicians, and these adverse events should be taken into consideration.

Published online: September 10, 2020.

Potential conflicts of interest: None.

Funding/support: None.

Patient consent: Permission was obtained from the patient to publish the case report, and information was de-identified to protect anonymity.

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