The ToxIC NOSE (Novel Opioid and Stimulant Exposure)

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Buprenorphine Associated Precipitated Withdrawal in the Age of Fentanyl

Introduction

The emergence of fentanyl as the dominant illicit opioid has transformed the management of opioid withdrawal and opioid use disorder (OUD).

Both heroin and fentanyl are full mu-opioid receptor agonists, but they differ in several aspects. Fentanyl is more lipophilic than heroin and accumulates within the subcutaneous fat, leading to a slow release from the body.[1] Fentanyl is shorter acting than heroin, and therefore needs to be used more frequently for a similar desired effect, or more commonly to prevent withdrawal symptoms.[2] This pattern of illicit fentanyl use prolongs the time it takes for the excretion of fentanyl, as highlighted by urine drug screens for fentanyl remaining positive for an average of 7 days in frequent users.[1]

Buprenorphine is a partial mu-opioid receptor agonist and has risen as a first-line treatment for OUD. The first dose is given to patients who are experiencing withdrawal symptoms after cessation of opioid use. In a person that reports regular use of heroin, buprenorphine can safely

be started within 12 hours of last use.[3] In those who use fentanyl, severe withdrawal symptoms must occur prior to starting buprenorphine due to the higher incidence of precipitated withdrawal.[1,3] This waiting period prior to starting buprenorphine may be 24-48 hours after last use. Though patients may report heroin only use, heroin is more frequently adulterated with fentanyl, or substances erroneously sold as heroin now contain only fentanyl.[4] Thus, patients that report heroin only use are more likely to be unintentionally exposed to fentanyl. Induction of buprenorphine in all OUD patients due to fentanyl exposure has led to warnings to wait for significant withdrawal prior to buprenorphine initiation to avoid inducing precipitated withdrawal.

There are several proposed hospital protocols for buprenorphine induction, including "micro induction" strategies that aim to minimize precipitated withdrawal by tapering from a full-opioid agonist, such as pharmaceutical fentanyl, to the partial opioid agonist buprenorphine.[7] This tapered approach slowly replaces the full opioid agonist with a partial agonist, preventing sudden withdrawal symptoms.

Unlike buprenorphine, methadone is a full mu-opioid agonist. Severe withdrawal symptoms prior to starting methadone are not necessary, and there is no risk of precipitated withdrawal associated with starting methadone.[5] Though these attributes are positive, methadone has drawbacks. Methadone toxicity causes respiratory depression and cardiotoxicity, and there are more fatalities associated with methadone use than buprenorphine use.[6] Due to these concerns, methadone is dispensed to patients with OUD on a day-to day basis in the clinical setting. In addition, methadone clinics are sparse in some areas of the United States. The lack of clinics, the daily toll of getting methadone from a clinic, and the social stigma limits the start of methadone treatment for both the patient and clinician.

Recently, the ToxIC NOSE detected a case of severe and difficult to treat precipitated withdrawal after administration of buprenorphine in a patient with a history of fentanyl use.

Case Presentation

A 30-year-old male with a long-standing history of opioid use was admitted to the hospital for multiple infections, including septic arthritis and osteomyelitis. He reported smoking

approximately 60 tablets of "M30"[1*] containing illicit fentanyl each day prior to admission. Within 8 hours of hospitalization, he developed opioid withdrawal symptoms including anxiety, nausea, tachycardia, and hypertension. He was contemplating signing out against medical advice because of the severity of his symptoms. He was treated with 8 milligrams (mg) of buprenorphine, in addition to benzodiazepines and antiemetics. However, within one hour he developed worsening symptoms of opioid withdrawal and was given an additional 8 mg of buprenorphine. After the 2nd dose of buprenorphine, the patient had severe precipitated withdrawal symptoms characterized by agitation, muscle aches, diaphoresis, diarrhea, nausea, vomiting, hypertension, and tachycardia. The medical toxicology physician was subsequently consulted for management of the patients precipitated withdrawal to facilitate urgent surgical procedures. Full opioid agonists were started by the medical toxicologist to help with the precipitated withdrawal. Over the next three hours he received a total of 7 mg hydromorphone along with 5 mg diazepam, 0.1 mg clonidine, and 4 mg loperamide. Despite this, he remained in severe withdrawal with a Clinical Opiate Withdrawal Scale (COWS) of 14 for restlessness, irritability, muscle aches, nasal drainage, diaphoresis, and tachycardia. He then received a total of 500 micrograms (mcg) of fentanyl (administered as 100 mcg per dose given over the subsequent three hours) after which his COWS score improved to 3. Throughout the night on hospital day one, he developed recurrent withdrawal symptoms and uncontrolled pain in his knee which were treated with hydromorphone and fentanyl. He received an additional 10 mg of hydromorphone and 600 mcg of fentanyl in the next twelve hours with variable control of his withdrawal symptoms (COWS scores ranged from 2-12). After returning from the operating room where he received irrigation of his infected joint, he again developed severe uncontrolled withdrawal with COWS scores ranging from 11 to 15. He was started on a fentanyl patient-controlled analgesia (PCA) pump and over the next 20 hours was titrated up to a dose of 200 mcg/hr with an additional 200 mcg bolus every hour for a total of 400 mcg/hr. He was also given adjunctive therapy with clonidine 0.2 mg three times a day, ondansetron, ibuprofen, and acetaminophen. At this fentanyl dose he remained awake and alert with spontaneous breathing and mid-sized pupils. Withdrawal symptoms stabilized on hospital day five. He was ultimately transitioned from the fentanyl infusion to oral methadone therapy and was discharged from the hospital to a long-term acute care facility.

Discussion

This case demonstrates many pitfalls of treating severe fentanyl withdrawal and initiating medications for OUD in hospitalized patients who have been using high daily doses of illicit

[1*] M30 pills are counterfeit pills that are made to resemble oxycodone, but typically contain fentanyl. Pills are round, light blue, and have an "M30" stamped onto one side of the pill. https://www.dea.gov/sites/default/files/2021-05/Counterfeit%20Pills%20fact%20SHEET-5-13-21-FINAL.pdf

fentanyl. Whereas intravenous pharmaceutical fentanyl administered for treatment of acute pain has a short duration of action, prolonged frequent use of illicit fentanyl pills, can lead to drug accumulation in peripheral tissues with prolonged effects.[1] This introduces increased complexity when initiating a patient on buprenorphine for treatment of opioid use disorder.

Buprenorphine acts as a partial mu-opioid receptor agonist, thus it can precipitate withdrawal symptoms in patients who are acutely under the effects of opioids. In patients using heroin, buprenorphine-induced precipitated withdrawal is not expected after 12 hours of abstinence.[1] The risk of developing severe precipitated withdrawal increases when buprenorphine is started within 48 hours after a patient's last fentanyl use.[8] Unfortunately, patients will often begin to experience opioid withdrawal symptoms long before this time point, and those symptoms are frequently refractory to treatment with non-opioid adjunct medications. As demonstrated by this case, such patients may require prolonged hospitalization for more complex management of their OUD with full opioid agonists with the hope that they can bridge to buprenorphine. However, ultimately some patients may not transition to buprenorphine despite intense efforts to do so. The challenge for clinicians is to be aware of the risk of precipitated withdrawal in patients using fentanyl, and to consider treatments beyond more standard buprenorphine induction, including various micro induction protocols and use of full opioid agonists, when appropriate.

Conclusion

Prolonged, frequent illicit fentanyl use can put hospitalized patients at risk for severe, precipitated, and refractory withdrawal, in particular when standard doses of buprenorphine are used early in the withdrawal syndrome.

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