Xylazine: a confounding adulterant

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Case Introduction

A 32-year-old male arrives via EMS after a suspected opioid overdose. Four milligrams of intranasal naloxone were administered in the field with limited effect. You note the patient has bradycardia and bradypnea with shallow respirations, and pulse oximetry shows an oxygen saturation of 85% on room air. The patient is hypotensive and exhibits minimal responsiveness to sternal rub. You also note that he has miotic pupils on physical examination. He is placed on 4 liters of oxygen by nasal cannula, and an additional two milligrams of intranasal naloxone are administered upon arrival, with some improvement in the respiratory rate and volume but no substantial improvement in mental status or blood pressure. After an additional 4 milligrams of IV naloxone is administered with oxygenation of 95% but persistent somnolence, you begin to suspect this is not straightforward opioid intoxication. What could explain the patient's persistent somnolence, and what would the next steps in management be?

Background

Xylazine has been reported as a heroin adulterant in Puerto Rico as early as the 2000s and is becoming more prevalent in overdose mortalities across the United States; it was found to be present in 25.8% of overdose deaths in Philadelphia in 2020 [1]. In Maryland (2021), Cook County, Illinois (2021), and Connecticut (2020), xylazine was present in 19.3%, 12.2%, and 10.2 % of opioid or overdose deaths, respectively [1, 2]. Massachusetts only began testing for xylazine in opioid overdose deaths in June of 2022 and has since reported its presence in 5% of opioid-related overdose deaths [3]. In Maryland, samples tested from participants in a needle exchange program who thought they were purchasing heroin or fentanyl found that 85% of the samples contained xylazine and were exposed to it unknowingly [4].

Ethnographic Data

Reyes et al. reported users in Puerto Rico endorse a longer duration of intoxication as compared to heroin use alone [5]. In Philadelphia, opioid formulations containing xylazine have been sought after due to increasing the duration of intoxication and euphoria as an answer to fentanyl's relatively short duration of effect and fentanyl's predominance in the illicit opioid supply [1]. Some users of xylazine adulterated opioids noted a dry mouth and a characteristic taste immediately after injection. Anecdotally, frontline providers have noted patients to be less responsive to naloxone than expected [1].

Pharmacology

Xylazine is a potent centrally acting α_2-adrenergic agonist that decreases the presynaptic release of norepinephrine and dopamine, resulting in sedation, muscle relaxation, and decreased perception of painful stimuli [6]. The CNS depression appears to be mediated only through a dose-dependent α2-adrenergic agonistic that does not involve cholinergic, dopaminergic, serotonergic, or histaminergic pathways [7]. People can use it intravenously, insufflation, or by injecting it into subcutaneous or intramuscular tissue[6, 8].

Commented [BM1]: what is his oxygenation?

Commented [BM2]: Add a question about what the reader feels is happening and what the next steps in management would be.

Commented [BM3]: While this would be accurate, correction of CNS depression is not the goal of mu-agonism reversal; it is the correction of respiratory depression, which you indicate has improved. If they are breathing and maintaining oxygenation, even with the aid of a nasal cannula, I don't know what the point of further naloxone would be. Over-reversal can lead to withdrawal, which is cruel, potentially dangerous, and unnecessary.

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Commented [BM5]: I would add a citation about the short duration of action, and also would comment that fentanyl has become the dominant form of opioid use. Otherwise, you have to include morphine and heroin.

Commented [BM6]: This is an awkward sentence, and I am unsure what you are trying to say. Please reword.

In a total of 104 postmortem cases where xylazine was detected in addition to a mu-receptor agonist, concentrations ranged from trace to 200 nanograms per milliliter [6, 9, 10]. In a mouse model, xylazine lethal dose (LD_{50}) was determined to be 157.2mg/kg. Still, when combined with 56mg/kg of fentanyl, the LD_{50} of the xylazine decreased to 32.0mg/kg, reflecting a potentially synergistic interaction between the drugs [11]. The change from 157mg/kg to 32mg/kg represents a nearly 80% decrease in the concentration associated with the death of 50% of the population. However, Love et al. reported a decreased rate of CPR and comas in combination opioid and xylazine overdoses, with no difference in mortality, ICU admissions, or emergency department discharges, indicating the need for further studies to characterize their interactions [12]. There is scant data for xylazine-only overdoses, but In an intentional intramuscular xylazine-only overdose, the patient's plasma concentration was determined to be 4600 ng/mL and the patient survived and was discharged on hospital day four [13].

Commented [BM7]: Put this into context. What is an LD50, and what is a typical lethal concentration? I would imagine there is more information about postmortem concentrations outside of these seven cases.

Toxidrome

Toxicity is similar to other centrally acting alpha-2-adrenergic agonists and includes central nervous system depression, miosis, bradypnea or apnea, bradycardia, hypotension, hypothermia, and dry mouth [14]. Other presenting symptoms, such as hyperglycemia, areflexia, asthenia, ataxia, blurred vision, disorientation, dizziness, and dysarthria, have also been reported [6]. Symptoms typically resolve in 25 to 72 hours [8].

Skin ulcerations have been noted in individuals who chronically inject xylazine in both Puerto Rico and Philadelphia [5, 6, 15]. The proposed mechanism is direct vasoconstriction of peripheral blood vessels, resulting in decreased skin perfusion and poor tissue oxygenation. [5, 16]. In a human model, it was demonstrated that centrally administered dexmedetomidine led to peripheral vasoconstriction via alpha(2)-adrenoceptor agonism [17], which could explain ulcerations located in areas not used for injection [16]. Some cases have required surgical debridement for treatment [11]. While withdrawal from xylazine is difficult to separate from opioid withdrawal, due to its similarity with clonidine and guanfacine, withdrawal from xylazine is suspected to be characterized by restlessness, rigors, and dysphoria, as noted in one case report [15].

Commented [BM8]: This is excellent, but please let's go one step further as the audience is primarily toxicologists; what is the mechanism of vasoconstriction?

Management

There is no known antidote for xylazine toxicity, and treatment is supportive. Naloxone may have some effect on central nervous system depression and is occasionally attempted in patients with clonidine toxicity [14]. Additionally, naloxone should be administered to reverse the likely opioid co-ingestion. Hypotension should be treated with intravenous fluids; however, if not effective, vasopressors may be necessary [8]. Atropine may be used if symptomatic bradycardia is present [18]. One of the first cases of xylazine withdrawal from chronic, known opioid and xylazine use was managed initially in the intensive care unit with a dexmedetomidine infusion, an 8mg/kg phenobarbital loading dose, followed by an initial trial of tizanidine before transitioning to clonidine. The patient was subsequently discharged on buprenorphine and clonidine [15].

Case Conclusion

You return to your patient after initiating intravenous fluids. The patient is now saturating 99% on room air; although the patient remains somnolent and bradycardic with borderline blood pressure, they appear to be perfusing their extremities adequately. You continue to observe them, and over 12 hours,

their vital signs and mental status improve. Once more awake, the patient tells you they had been using what they thought was fentanyl, but their friends had heard rumors of a batch of “tranq” or “tranq-fent” being distributed in the area, slang for a mixture of the xylazine and fentanyl [1].

Uncategorized References

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