Xylazine toxicity

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ABSTRACT

Xylazine is a structural analog of clonidine and is an alpha-2 adrenergic receptor agonist. It is used in veterinary medicine for sedation, anesthesia, muscle relaxation, and analgesia, and it is often used with ketamine for anesthesia. Illicit drug use and overdose can result in severe mental and/or physical toxicity, including hallucinations, incoherent thought processes, hypotension, and skin necrosis. Detection is often difficult because xylazine is not identified in most drug screens used in emergency departments. There is no specific treatment except for supportive care. Clinicians should consider xylazine toxicity in patients admitted to intensive care units with non-specific clinical presentations, especially if they have unexplained skin ulcers and necrosis.

Keywords: xylazine, toxidrome, skin necrosis, tranq.

INTRODUCTION

Xylazine is a structural analog of clonidine and is an alpha-2 adrenergic receptor agonist. Its formula is $C_{12}H_{16}N_2S$; its molar mass is 220.33 grams/mole. It is used in veterinary medicine for sedation, anesthesia, muscle relaxation, and analgesia, and it is often used with ketamine for anesthesia. In larger mammals, the half-life of xylazine is 1.2 to 5.9 minutes, and it has a large volume of distribution. It is lipophilic and directly stimulates central alpha-2 adrenergic receptors and peripheral alpha-2 adrenergic receptors. As an agonist, it reduces the release of norepinephrine and dopamine in the central nervous system (CNS) because it binds to presynaptic surface receptors, which in turn inhibit norepinephrine release. This review covers critical features of xylazine toxicity in intensive care unit patients.

DISCUSSION

Xylazine has become a popular street drug in some parts of the United States and is known as *tranq* or *tranq de caballo.* It is commonly used as an additive with fentanyl for enhanced drug effect or as a cheap adulterant to increase drug quantity. Many fentanyl users are unaware that xylazine is mixed with fentanyl. Xylazine can be inhaled or administered intravenously, intramuscularly, subcutaneously, or orally. Its effect usually occurs in 15 to 30 minutes and sedative effects may continue for 1 to 2 hours and up to 4 hours. In nonfatal overdoses the blood concentration ranges from 0.03 to 4.6 mg/L. It is metabolized in the liver and then excreted in the urine. Xylazine toxicity can include sedation, dysarthria, hyporeflexia, disorientation, hypotension, and bradycardia. When combined with other CNS depressants, it can cause severe CNS depression with obtundation and coma. Chronic use of this drug can cause skin ulcers, abscesses, and infections. These can lead to systemic consequences. This drug is not detected by the most frequently used urine drug screening tests. Advanced testing such as liquid chromatography-mass spectrometry (LC-MS) is required, but it is not widely and immediately available.

Cano et al., analyzed the frequency of xylazine-related deaths and found an increase between 2019 and 2022.[1] The highest rates were in Vermont at 10.5 per 100,000 residents and in Connecticut at 9.8 per 100,000 residents. Information collected from the National Forensic Laboratory Information System demonstrates

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that there is significant variability among states with the identification of xylazine in the reports. For example, xylazine was present in 16.2% of all reports in Delaware but in less than 1% of reports in 35 different states. This study demonstrates that xylazine related overdose tests are relatively high in only certain communities but its use is increasing throughout the United States, and it is likely underestimated due to limited testing. In particular, xylazine is frequently combined with fentanyl.

Gupta et al., reviewed xylazine in 2023.[2] It was approved for veterinarian use in 1972. Its effects in the central nervous system include sedation, analgesia, and euphoria. It does cause addiction in humans, and some individuals have severe withdrawal symptoms when it is discontinued. It can be ingested, or smoked, or snorted, or injected intramuscularly or intravenously. Patients who present with xylazine intoxication have central nervous system depression, hypotension, and bradycardia. However, they often have injected xylazine with other drugs, and their presentation varies depending on the combination of drugs used. It is associated with severe necrotic skin ulcerations. These can occur regardless of the method of administration and can occur at sites other than injection sites. Due to alpha 2 adrenergic property of the drug, it causes local vasoconstriction reducing blood flow to the skin and subcutaneous tissue leading to tissue hypoxia, which can result in necrosis even in the absence of infection and poor wound healing. Xylazine may also cause direct dermal toxicity.

Retrouvey et al., reviewed the management of 20 cases of soft tissue necrosis secondary to xylazine use.[3] The seven patients in their personal case series included five men and two women. Their wounds were located on the forearm and hands, and their duration ranged from 5 days to 2 years. These cases needed local wound care with surgical debridement, soft tissue reconstruction with skin grafting, osseous reconstruction, and limb amputation. When their seven cases were included with the 20 total cases from the literature review, 10 of 20 patients required amputation. The management strategy depended on the depth of the wound. Xylazine has potent vasoconstrictor activity that can lead to tissue ischemia and eventually necrosis. Repeated episodes of trauma contribute to the tissue damage, and self-management of localized infections also contributes to poor outcomes. Figure 1 illustrates a typical xylazine related necrotic skin ulcer.

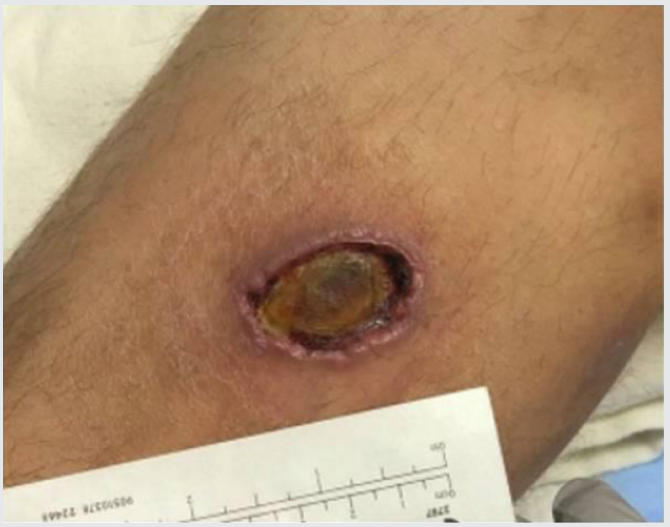

Figure 1. A man with a history of IV drug use and hepatis C presented with a spreading, painful area on his right medial thigh. He had a longstanding history of IV cocaine and fentanyl use and last injected fentanyl 1 week prior. He believed the fentanyl contained xylazine, as the last dose of fentanyl was "more potent" than prior doses. Toxicology screen was positive for cocaine and fentanyl, and urine xylazine analysis was positive at 40,000 mg/mL. Necrotic ulcers at previous injection sites were observed on his arms, hands, legs, and feet. Punch biopsy showed nonspecific inflammation and subcutaneous necrosis, without vasculopathy. Tissue cultures were positive for 1 colony of streptococcus and cultibacterium, which were considered contaminants. His clinical presentation was consistent with xylazine-induced skin necrosis. He received local wound care with significant improvement. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10242481/figure/fig2/). Accessed-2-10-2025. https://www.wikimedia.org/.

The behavior of individuals who use xylazine chronically and develop skin ulcers contribute to the public perception that these individuals exhibit a "zombie" phenotype. Acute neuropsychiatric side effects of xylazine are deep sedation often resembling

opioid overdose but typically unresponsive to naloxone. Patients may present in a comatose state requiring airway protection.[4] Cognitive disorientation and transient amnesia are frequently noticed, and these symptoms may last longer after initial sedation is weaned off.[5] While recovering from sedation, patients may have precipitating delirium agitation, hallucinations, and incoherent thought processes.[6] Chronic neuropsychiatric sequelae include depression and/or suicidal ideation.[7] Chronic ritual use can potentially lead to cognitive deficits likely related to neurochemical disruptions secondary to hypoxemic episodes. Psychosis, including paranoia and hallucinations, have been documented especially during periods of withdrawal and in people with high cumulative exposure.[8] Xylazine's pharmacological effect is to inhibit norepinephrine release; indirectly, dopamine and serotonin may contribute to mood alternating behavior and may reinforce drug taking. Its addictive potential is similar to that of sedative hypnotics such as benzodiazepines.

Some users report using xylazine to enhance the effect of opioids leading to dependance. Repeated exposure causes changes in GABA and glutamatergic neurotransmission similar to the effects of alcohol and benzodiazepines.

Diagnosis of xylazine overdose is clinical, based widely on clinical presentation and geographical areas in which tranq use is suspected. Management is most likely supportive care, airway protection, oxygen supplementation, and mechanical ventilation if needed. Drug management includes vasopressor support in cases of hypotension, and atropine may be used in profound symptomatic bradycardia. Naloxone administration should be used if opioid co-ingestion is suspected, but it does not reverse xylazine effects. Continuous critical care monitoring may be necessary in severe cases. Some experimental approaches considered alpha 2 adrenergic antagonists (yohimbine) to help with withdrawal symptoms. No formal validated studies have been published regarding this.

Complications secondary to xylazine may include death from respiratory failure, hypoxic brain injury due to prolonged apneas, severe infections, and necrotic skin ulcers due to tissue toxicity.

Conclusion

Xylazine, originally a veterinary sedative, is increasingly becoming a public health concern due to its illicit use especially in combination with other drugs. Its alpha-2 adrenergic activity causes profound sedation, cardiovascular depression, and neuropsychiatric disturbances. Alarming chronic complications are skin necrosis and addiction potential that complicates management. Lack of specific detection methods and specific antidotes further challenges intervention. The severe toxicity associated with xylazine overdoses underscores an urgent need for expanded surveillance, public education, and development of evidence-based management strategies. Prompt recognition and supportive care remain the cornerstone of treatment, but long-term solutions will require a multidisciplinary approach involving clinicians, toxicologists, public health authorities, and policymakers.

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