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Xylazine: A Deadliest Drug

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ABSTRACT

Xylazine is a white, crystalline chemical with a bitter taste that is readily soluble in water. Its chemical composition is comparable to that of clonidine, tricyclic antidepressants, and phenothiazines. It is a non-narcotic medication used alone or in conjunction with other medications to sedate, anesthetize, or generalize anesthesia in animals. It is a US-FDA-approved drug. It causes drowsiness, muscular relaxation, and a decrease in the perception of painful stimuli because it decreases the release of noradrenaline and dopamine in the central nervous system. Investigations of xylazine in people were conducted, however it was not used because of serious hypotension. In this review article, we are dealing with xylazine toxicity and treatment.

INTRODUCTION

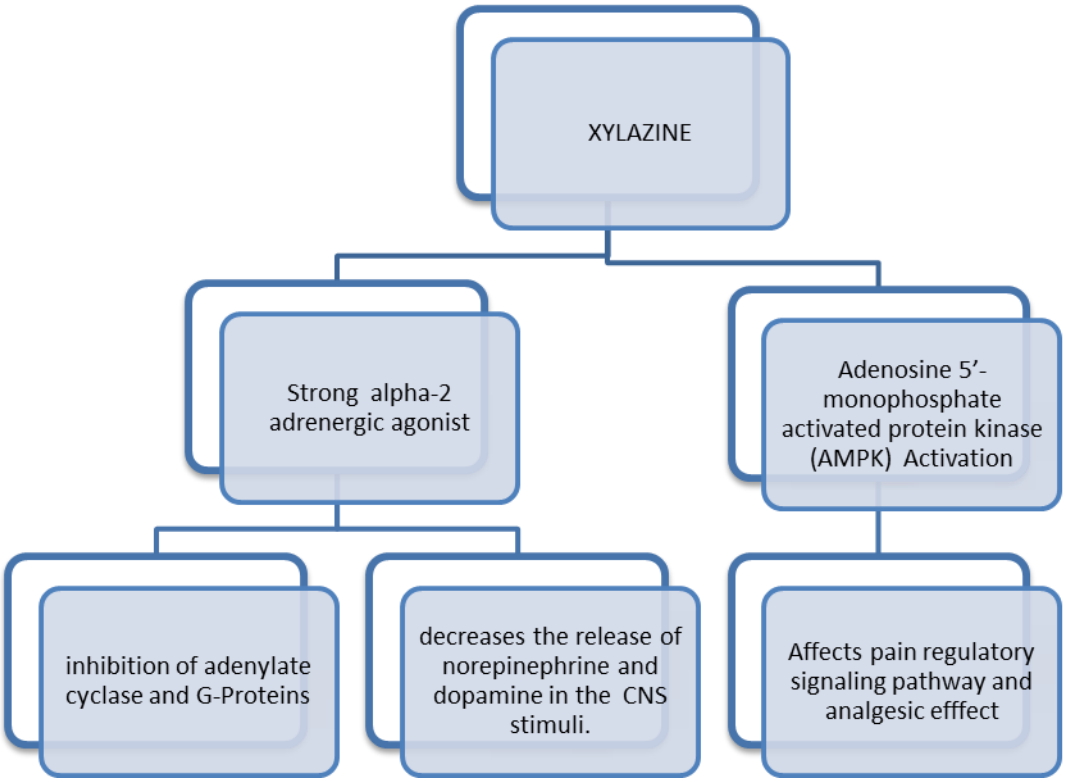
XYLAZINE-

Xylazine is a veterinary sedative, analgesic, or general anesthetic. Its pharmaceutical action results in sympathetic discharge via stimulation of alpha-2-adrenoceptors.[1-3] Xylazine can be administered using intravenous, intramuscular, or subcutaneous methods on animals. Its dosage ranges from 0.5 mg/kg to 5.0 mg/kg administered intravenously or orally, and It has a limited therapeutic index.[4] More than twice or three times the recommended therapeutic dose may be fatal. Although xylazine use in humans was examined, it was avoided because of severe hypotension. Xylazine is broken down in the kidney, where it is eliminated 70% through the kidney and 30% through the bile. Intact xylazine is excreted in just 8% of cases. Within 10 to 15 hours, the entire drug is excreted.[5-6]

Xylazine initially increases blood pressure; but, over time, it causes permanent hypotension, bradycardia, and a decrease in cardiac output, with the central nervous system's alpha-2 receptors being predominately blocked. The FDA has not given Xylazine its approval for use in humans. Its application as a sedative-hypnotic, analgesic, and anesthetic medication in humans was examined, but it was abandoned due to its frequent correlation with severe hypotension and central nervous system depression.[7]

It inhibits the brainstem vasomotor center through the alpha-2 agonist action. Alpha-1 adrenergic, histaminergic, cholinergic, serotonergic, dopaminergic, serotonin, serotonin, and opiate receptors may also have affinities. It decreases the amount of noradrenaline and dopamine released into the central nervous system, which causes drowsiness, muscle relaxation, and a lessened sense of painful stimuli.[8]

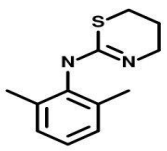
Mechanism of action-



Xylazine is a strong α2-adrenergic agonist whose effects are mediated via stimulation of central α2-receptors. α2-adrenergic stimulation decreases the release of norepinephrine and dopamine in the central nervous system (CNS) resulting in sedation, muscle relaxation, and decreased perception of painful stimuli.[2,9]

Moreover, it also affects cholinergic, serotonergic, dopaminergic, 1-adrenergic, histaminergic, or opiate processes. Rapid absorption, metabolism, and elimination all occur with xylazine. xylazine uncharged, lipophilic nature, it diffuses widely and crosses the blood-brain barrier as expected. When taken orally, xylazine and other 2-adrenergic receptor agonists spread throughout the body in 30 to 40 minutes. The sedative and analgesic properties of xylazine prevent the CNS from receiving and transmitting neural impulses. Xylazine reduces norepinephrine and dopamine neurotransmission hence it is an agonist.[10]

XYLAZINE STRUCTURE-



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CASES OF XYLAZINE-

CASE-1-

The emergency team discovered the 24-year-old veterinarian physician, who weighed 110 kg (242 lb), at home, sprawled on the lavatory floor. He called his friend and threatened to terminate his life. His medical background was unremarkable. We were the only ones who knew he smoked and drank in public. He was transported by ambulance to our emergency room while he remained unconscious. According to information from his companion, he may have injected himself with a suicide intent one vial of xylazine (500 mg) intravenously. It was also discovered that he had previously made many attempts at suicide using different substances. On his arm, there was evidence of an injection.

His medical examination revealed that he was unconscious, with a GCS of 3, and that neither his blood pressure nor his pulse could be detected. The patient was being watched; the monitor showed consistent, pulseless electrical activity at a rate of 122/min, and the patient's oxygen saturation was 80%. He was given CPR because the lack of electrical pulses indicated that he was in a state of cardiac arrest. The patient experienced ventricular fibrillation during the initial stages of resuscitation; as a result, he was defibrillated. Asystole became the rhythm during resuscitation. Ninety minutes later, the patient was deemed dead since he or she was not responding to further resuscitation efforts.

CASE-2-

About public health, safety, and criminal investigation, xylazine is an emergent adulterant alongside fentanyl in deadly drug intoxications. Only in veterinary medicine is the non-narcotic sedative xylazine used for analgesia and muscular relaxation. It has a molecular structure akin to clonidine and functions as a central -2 agonist, which may result in

bradycardia and briefly elevated blood pressure that quickly drops. From March through August 2019, 42 deaths in Connecticut were found to have xylazine in their systems. The toxicity of an opioid or stimulant may change when taken with xylazine. When xylazine is found, forensic pathologists may be better able to distinguish between illegal and legally obtained fentanyl, and law enforcement officials may be able to trace illegal drugs back to a particular supplier. Emergency medicine doctors need to be aware of its probable presence since it may influence therapy due to its lack of reaction to naloxone.

RECENT RESEARCH ON XYLAZINE-

The inclusion of the chemical Xylazine, sometimes known as "tranq" or "tranq dope," in synthetic opioids like fentanyl, which causes significant skin degeneration in users, is raising concerns throughout the United States. However, there is not much information out there regarding Xylazine.[11]

This substance is wreaking havoc in major cities across the US and has devastating effects that can rot the user's skin. The substance is wreaking havoc in major cities across the US and has devastating effects that can rot the user's skin. Hence it is called as Skin rotting.[12]

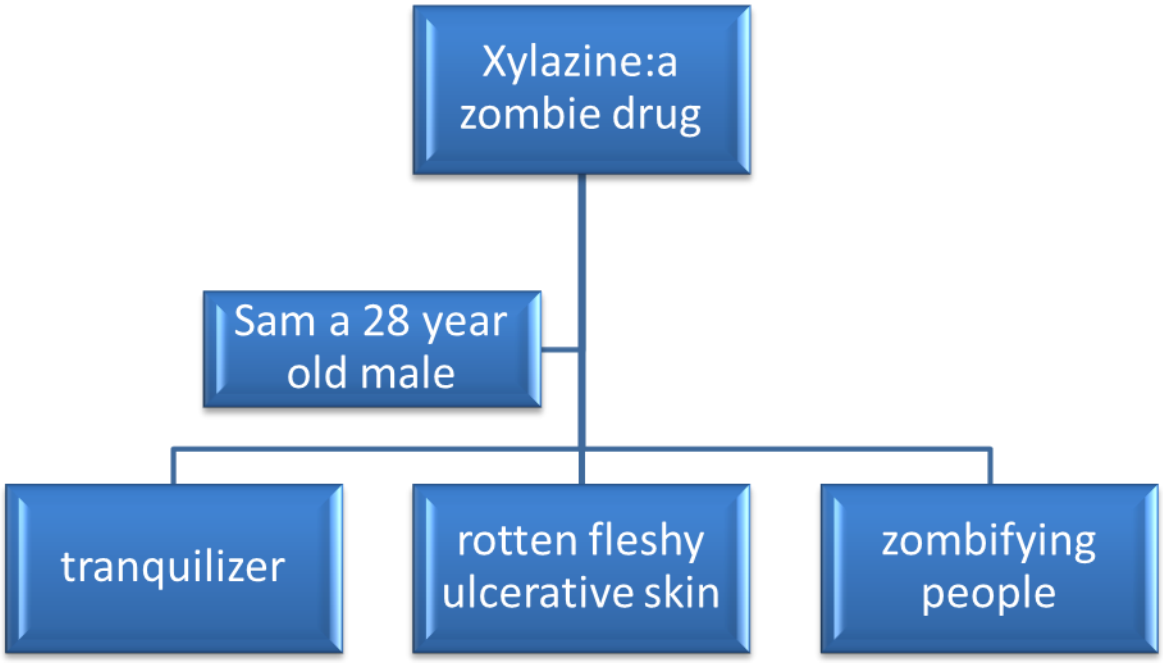
Horses and cattle are treated with the sedative xylazine. Repeated exposure can cause open wounds that can quickly become severe as well as sedative-like symptoms such extreme exhaustion and respiratory depression. If the crusty ulcerations are not treated, they may become eschar, or dead skin, and necessitate amputation.

In a sense, Tranq turns humans into zombies. I had never suffered any crusty ulceration wounds before nine months ago. Today, my legs and feet have holes in them, Sam, a 28-year-old male, told Sky News.[13,14]

Because xylazine acts as a tranquilizer, higher doses entirely knock users out. Fentanyl cut with xylazine may lead users to pass asleep and wake up many hours later, in contrast to opioids' blissful semi-awakeness.[15]

Xylazine:A Zombie drug-

The "zombie drug" seemed to first appear in Philadephia, before migrating west to San Francisco and Los Angeles. It was used in cutting heroin and now has been discovered in fentanyl and other illicit drugs.[11]



Adverse effect of xylazine -

Common side effects of xylazine-

- Blurred vision
- Disorientation
- Sedation
- Drowsiness
- Slurred speech
- Impaired judgment
- Hypotension

- Coma
- Bradycardia
- Respiratory depression
- Pinpoint pupils
- Hyperglycemia (high blood sugar)

The adverse effects are due to Overdose of xylazine which shows reports of xylazine medication consumption in non-fatal human instances ranging from 30 to 4,600 ml. The doses of xylazine used in fatal overdose cases reached 16,000 ml. Xylazine overdoses require emergency medical assistance, much like overdoses from other drugs[9].

Adverse effects are bradycardia, hyperglycemia, reduced heart rate, hypothermia, coma, respiratory depression, and dysrhythmia and may cause physical dependence.

Its withdrawal symptoms are more dangerous than heroin and methadone, it include sharp chest pain and seizures.[7,8]

Intramuscular injection of xylazine, being an alkaloid substance, it was found to be present on large amount in gastric juice causing gastric lavage.

DRUG INTERACTION-

It has been demonstrated that the toxic effects and fatality rate of xylazine increased when it was combined with ketamine, heroin, or alcohol. It is proposed that comparable The synergistic pharmacological actions of xylazine and heroin exacerbate the toxicity.

Combination of metoclopramide and xylazine at the level of visceral and central analgesia in mice. Low doses of both medications together result in excellent, secure analgesia that has applications in veterinary medicine.[4,6]

TREATMENT-

No antidote is present for humans. Yohimbine, tolazoline, and other alpha-adrenergic antagonists were proposed as xylazine antidotes; however, they were not tested on people.

The importance of supportive care in the treatment of xylazine overdose is substantially greater. Oxygenation, endotracheal intubation when necessary, intravenous fluid infusion, gastric lavage, active charcoal, urine catheterization, electrocardiography (ECG), and monitoring of hyperglycemia are all examples of supportive treatment. Treatment with hemodialysis is ineffective.

Patients having xylazine addiction can joined opium addiction treatment program.[2,4]

CONCLUSION –

Xylazine is a prescription medication used to sedate, anaesthetize, relax muscles, and relieve pain in non-human mammals like horses, cows, and other animals.

Xylazine is FDA-approved for use in animals as a sedative and pain reliever. It can be challenging to discern between opioid overdoses and xylazine exposure because xylazine is not safe for usage in humans and may cause serious and perhaps fatal side effects.

REFERENCES-

1. Greene SA, Thurmon JC. Xylazine—a review of its pharmacology and use in veterinary medicine. J Vet Pharmacol Ther. 1988;11(4):295–313. doi: 10.1111/j.1365-2885.1988.tb00189.x.
2. Kitano T, Kobayashi T, Yamaguchi S, Otsuguro K. The alpha(2A) -adrenoceptor subtype plays a key role in the analgesic and sedative effects of xylazine. J Vet Pharmacol Ther. 2019;42(2):243–247. doi: 10.1111/jvp.12724. -
3. Bedard M, Murray J, et al. Xylazine is an agonist at kappa opioid receptors and exhibits sex-specific responses to naloxone administration. Preprint. Posted September 9, 2023. 10.1101/2023.09.08.556914
4. Ruiz-Colon K, Chavez-Arias C, Diaz-Alcala JE, Martinez MA. Xylazine intoxication in humans and its importance as an emerging adulterant in abused drugs: a comprehensive review of the literature. Forensic Sci Int. 2014;240:1–8. doi: 10.1016/j.forsciint.2014.03.015. -
5. Reyes JC, Negron JL, Colon HM, et al. The emergence of xylazine as a new drug of abuse and its health consequences among drug users in Puerto Rico. J Urban Health. 2012;89(3):519–526. doi: 10.1007/s11524-011-9662-6.
6. Rodriguez N, Vargas Vidot J, Panelli J, Colon H, Ritchie B, Yamamura Y. GC-MS confirmation of xylazine (Rompun), a veterinary sedative, in exchanged needles. Drug Alcohol Depend.2008;96(3):290–3. 10.1016/j.drugalcdep.2008.03.005
7. Alexander RS, Canver BR, Sue KL, Morford KL. Xylazine and overdoses: trends, concerns, and recommendations. Am J Public Health. 2022;112(8):1212–1216. doi: 10.2105/AJPH.2022.306881
8. Rock KL, Lawson AJ, Duffy J, Mellor A, Treble R, Copeland CS. The first drug-related death associated with xylazine use in the UK and Europe. J Forensic Leg Med. 2023;97:102542. doi: 10.1016/j.jflm.2023.102542.
9. Greene SA, Thurmon JC. Xylazine—a review of its pharmacology and use in veterinary medicine. J Vet Pharmacol Ther. 1988;11(4):295–313. doi: 10.1111/j.1365-2885. 1988.tb00189.x.
10. Mittleman RE, Hearn WL, Hime GW. Xylazine toxicity–literature review and report of two cases. J Forensic Sci. 1998;43(2):400–402. doi: 10.1520/JFS16155J.

11. Ruiz-Colón K, Chavez-Arias C, Díaz-Alcalá JE, Martínez MA. Xylazine intoxication in humans and its importance as an emerging adulterant in abused drugs: A comprehensive review of the literature. Forensic Sci Int. 2014; 240:1–8. doi: 10.1016/j.forsciint.2014.03.015.
12. Ball NS, Knable BM, Relich TA, Smathers AN, Gionfriddo MR, Nemecek BD, et al. Xylazine poisoning: a systematic review. Clin Toxicol (Phila) 2022;60(8):892–901. doi: 10.1080/15563650.2022.2063135.
13. Kacinko SL, Mohr ALA, Logan BK, Barbieri EJ. Xylazine: pharmacology review and prevalence and drug combinations in forensic toxicology casework. J Anal Toxicol. 2022;46(8):911–917. doi: 10.1093/jat/bkac049.
14. Ayub S, Parnia S, Poddar K, Bachu AK, Sullivan A, Khan AM, et al. Xylazine in the opioid epidemic: a systematic review of case reports and clinical implications. Cureus. 2023;15(3):e36864.
15. Thangada S, Clinton HA, Ali S, Nunez J, Gill JR, Lawlor RF, et al. Notes from the field: xylazine, a veterinary tranquilizer, identified as an emerging novel substance in drug overdose deaths—Connecticut, 2019–2020. Morb Mortal Wkly Rep. 2021; 70:1303–1304. doi: 10.15585/mmwr.mm7037a5.