XYLAZINE–ISN'T FENTANYL ENOUGH?

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BACKGROUND: XYLAZINE

- Non-opioid veterinary sedative/anesthetic that is not approved for use in humans due to profound sedation
- No clinically proven antidote or reversal agent.
- Alternative names:
  - Tranq
  - “Anestesia de caballo”
  - Zombie
  - Rompun
- Identified in Puerto Rico in early 2000s

History of xylazine

- Xylazine is a non-opioid used as a sedative, anesthetic, muscle relaxant, and analgesic for animals. It is a strong synthetic alpha-2 adrenergic agonist, synthesized in 1962 in Germany by Bayer as an anti-hypertensive, analgesic, hypnotic, and anesthetic. *It was not approved for human use due to severe CNS depressant effects*.
- A veterinary medication used for procedural sedation in both small and large animals (approved for veterinary use in the US by the FDA)
    - Not a controlled substance; not scheduled in the US as it is not intended for human use
    - When used in combination with opioids, enables use of lower doses of opioids and enhances both sedation and anesthesia
- Initially emerged sporadically in the literature as a substance of use in the 1980s and 1990s, emerged as a substance of widespread misuse in Puerto Rico in the early 2000s and was known as ‘anestesia de caballo’
    - Misuse first noted in Philadelphia in 2006

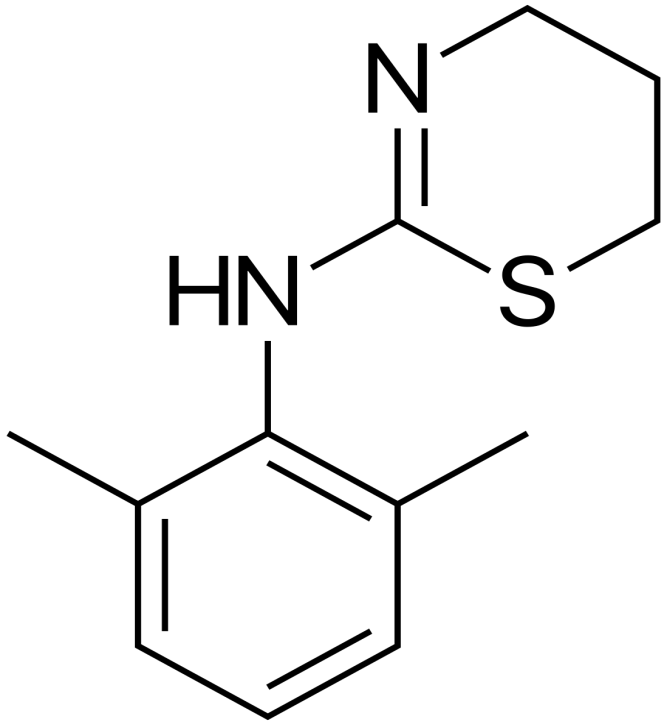
Xylazine: Structure, Pharmacology, and Clinical Effects

- Alpha-2 adrenergic agonist that *stimulates central alpha-2 receptors:*
  - Decreases sympathetic nervous system outflow

  -> sedation (decreases the release of NE and dopamine)

  - **CNS DEPRESSION:** ***No effect on respiratory rate, blunted response to airway occlusion (hypoxia) similar to other sedatives (benzodiazepines, barbiturates), synergistic effect with opioids***
- Similar effects to *imidazoline* compounds, such as clonidine, dexmedetomidine, oxymetazoline, tetrahydrazoline, tizanidine, and lofexidine
  - **Major clinical effect is profound sedation**
  - **But *NO* imidazoline receptor activity, so *NO* hypotension/bradycardia**
  - Increase in vagal tone is reported in the veterinary literature
  - Acts on alpha-2 receptors in pancreatic beta cells, inhibiting insulin release->hyperglycemia
  - One of xylazine's metabolites, 2,6-xylidine, has been classified as potentially genotoxic and carcinogenic in humans based on animal studies
- Pharmacokinetics:
  - Typical anesthesia dose ranges (0.2-1 mg/kg IM or IV)
  - Time to effect is 1-2 minutes (depending on administration route); lipophilic, diffuses widely, good bioavailability
  - Average duration of substance effect up to 4 hours, but can last longer
  - Routes of Administration: IV, IM, SC, PO, inhalation, insufflation, ocular

Xylazine Structure



Similar chemical structure to phenothiazines, TCAs, and clonidine

Thanks to Joseph D'Orazio, MD

Forensic Sci Int. 2014 Jul;240:1-8

BCCDC Harm Reduction Services, 1/24/22

ToxTalks, Blue Ridge Poison Center, 2/2022

ADULTERANTS

- A pharmacologically active substance that is added to a product
- Adulterants are intentionally added to drugs to increase bulk, enhance or mimic a pharmacological effect, or to facilitate drug delivery
- Xylazine may enhance euphoria, and extend sedation up to 4-8 hours
  - About 1/3rd of fentanyl users will seek out fentanyl containing xylazine, the remainder will try to avoid it (test strips will hopefully become available)
  - With profound sedation and immobilization, rhabdomyolysis possible with potential of myoglobinuria and possible ARF. Hydration, and potential hemodialysis may be required.

MIXED OVERDOSE COMPLICATES OVERDOSE MANAGEMENT WITH NALOXONE

- The respiratory depression due to fentanyl will respond to naloxone but the sedation caused by xylazine will not.
- “Establish respiration not conversation” Goal is acceptable pO2/O2sat. Maintain person in a rescue position.
- Excessive use of naloxone may exacerbate and prolong the naloxone precipitated withdrawal.
- Observation in a medical setting is required until sedation from the xylazine resolves and stable cognitively. Requires capability of providing MOUD in both ED and hospital units.
- Xylazine may be present in methamphetamine, and cocaine samples

TOXIDROME

Acute

- Prolonged sedation, blackouts
- Disorientation
- Drowsy
- Blurred vision
- Slurred speech
- Dry mouth
- Hypotension, bradycardia
- Muscle relaxation, respiratory depression

Chronic

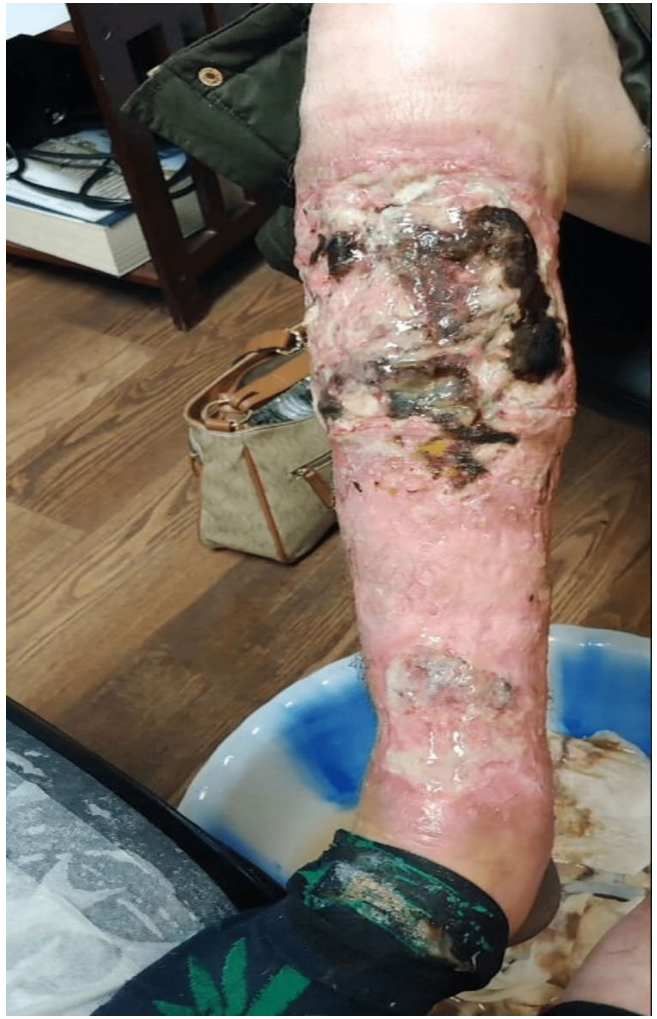
- Severe skin wounds
- Dysglycemia, abnormal blood sugar
- Anemia

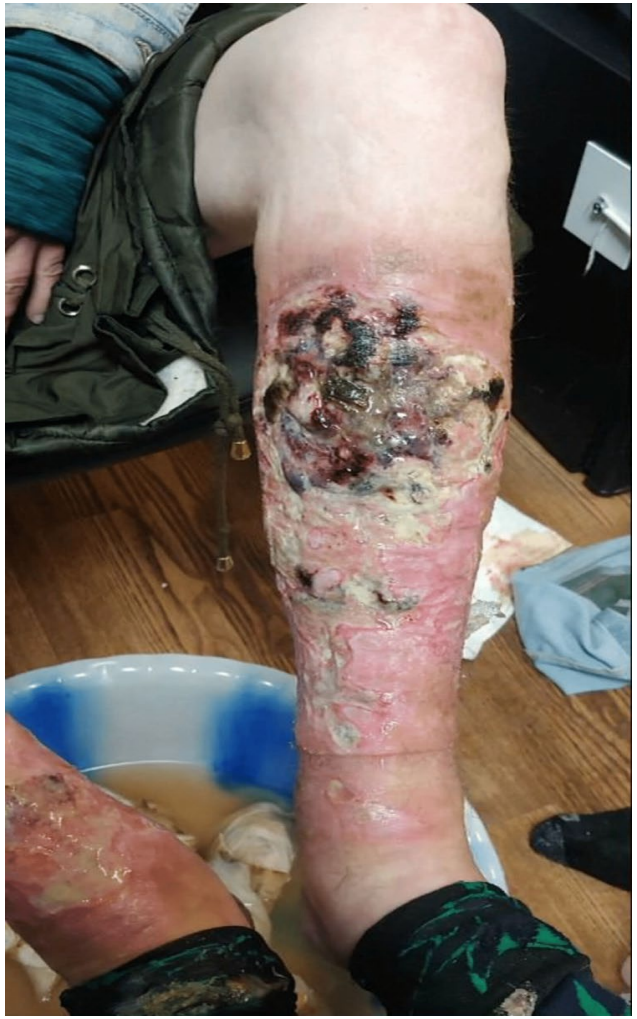
XYLAZINE WITHDRAWAL???

- Not a well-defined syndrome, but includes anxiety, irritability, and restlessness. Severe hypertension is possible, like with abrupt discontinuation of clonidine.
- Can, with mixed success manage with benzodiazepines and/or alpha-2 adrenergic agonists such as clonidine, dexmedetomidine, tizanidine, guanfacine.
- Treat opioid withdrawal early and effectively.

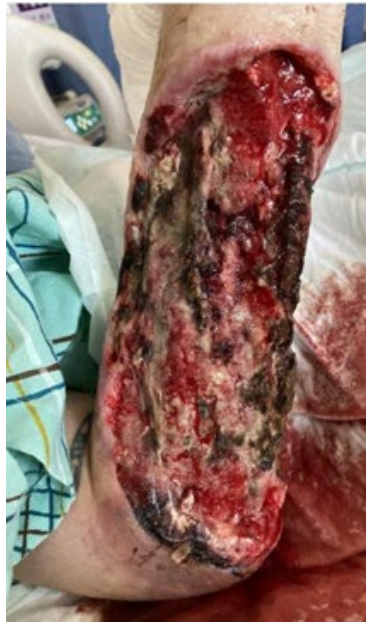
WARNING, THE FOLLOWING WOUNDS MAY BE DIFFICULT FOR SOME IF NON-MEDICAL!

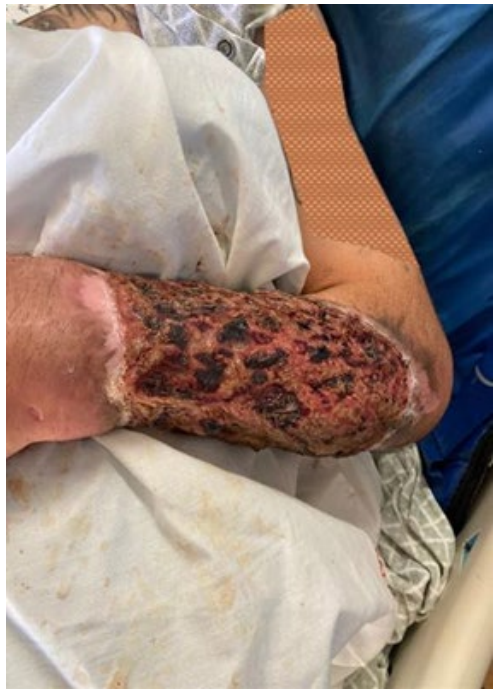
Differential?

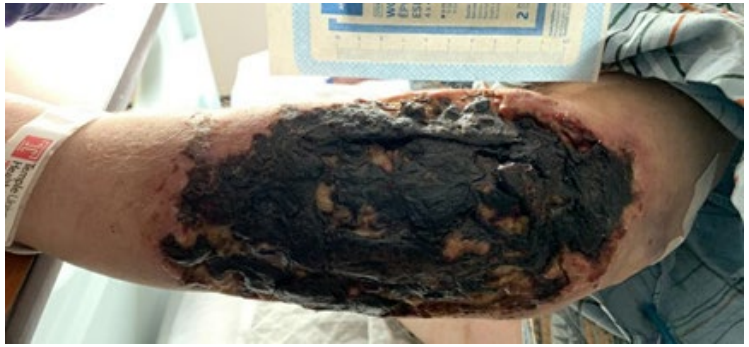


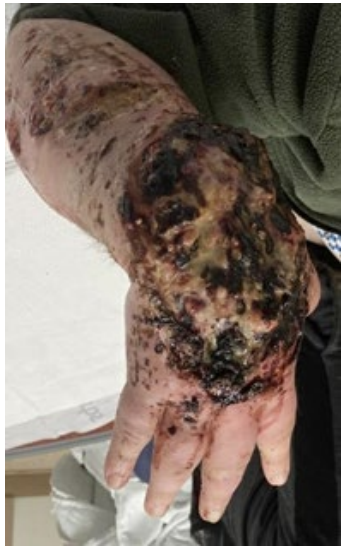


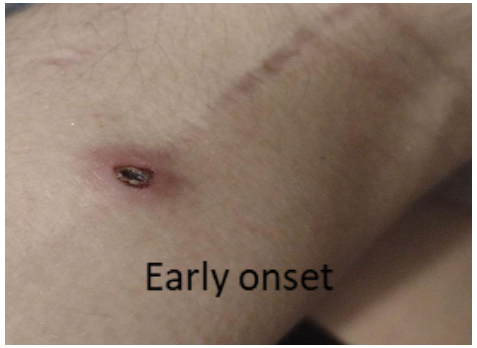
Xylazine and Skin Ulcers/Wounds

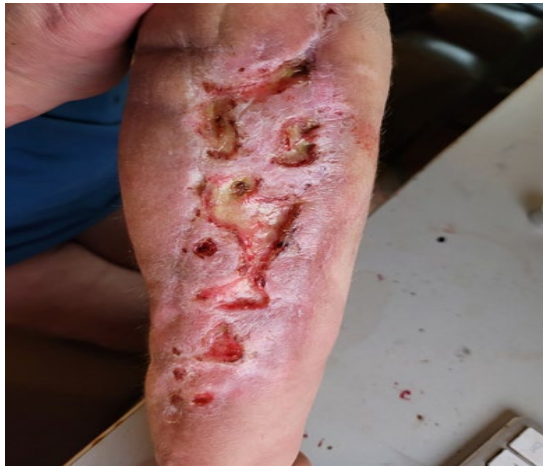


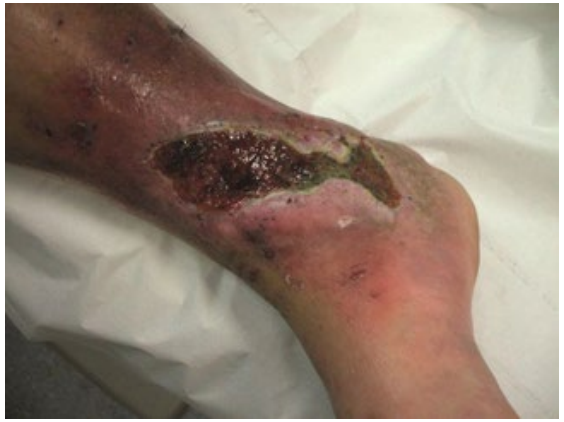












NHRC Xylazine Office Hours, 4/2022

Xylazine and Skin Ulcers/Wounds

- Severe necrotic skin ulcerations, often necessitating complicated wound care
- Occur at skin sites associated with injection, *but also at skin sites not associated with injection and in individuals who don't inject*
- The pathophysiological mechanism which causes the ulcerations is unclear; they are not infectious, but can become superinfected with bacteria, particularly with skin picking

FDA Dear Colleague Letter: FDA Warns About the Risk of Xylazine Exposure in Humans, 11/8/22

Wound care

- Avoid alcohol and hydrogen peroxide.
- Clean wounds with soap and bottled/tap water or saline.
- Cover with a non-adherent dressing (Xeroform) covered by an absorbent one.
- Keep skin around wound clean of drainage and moisturized (Vitamin A+D ointment).
- Goal for wound bed: keep moist (helps dead skin soften/fall on its own) or debridement.
- Antibiotics may not be needed.
- Manage pain.
- Sometimes amputation is required.

Harm Reduction Messages

Educate patients about xylazine in the drug supply and ask about wounds. Provide test strips if available.

Providers should be aware of the heightened risk of skin and soft tissue wounds, discuss injection techniques.

Educate regarding OD risks. Consider developing on site tox testing of samples.

Harm reduction

- Talk to potential users about xylazine in the supply, advise to seek other batches
- Ask about unusual wounds.
- Educate on “red flag symptoms”; fever, chills, skin turning black or dark
- Rotate sites, and avoid injecting groin and neck
- Wash hands and injection sites with soap and water or use alcohol pads
- Needle angle at 45 degrees, wipe needle with alcohol pad wiping any solution off prior to injection.
- Evaluate for infection ?systemic antibiotics, cleanse wounds, topical ointment, don’t scratch, A+D on healthier skin, non-adhesive dressings, debridement? Daily dressing changes.

Basic Harm Reduction

- Go slow, use less.
- Test product if you can.
- Sniffing or smoking is probably safer than injecting. Fatal Ods by inhalation/smoking now greater than by injection
- Avoid using alone.
- Carry naloxone and know how to use it. Look out for each other.
- Call 911, be aware that a xylazine overdose may need more than naloxone.
- Be sure airway is open, show rescue position.