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Case Report/Case Series

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# A case series of accidental xylazine intoxication in humans; Is there a role of naloxone as an antidote?

**Lee Kee Choon*, Ain Izzati Khiruddin, Wan Masliza Wan Mohd Annuar, Sazwan Reezal Shamsuddin**

*Department of Emergency and Trauma, Hospital Sultan Haji Ahmad Shah, Temerloh, Pahang, Malaysia*
**Corresponding author*

**Abstract:**

Xylazine is a type of sedative commonly used in veterinary medicine. It acts on the central alpha-2 receptor and suppresses norepinephrine release from the peripheral nerve terminal. It is also reported to have action on cholinergic, serotogenic, H2-histamine, dopaminergic, and opioid receptors. Once administered in animals, it causes hypotension, bradycardia, central nervous system depression, and respiratory depression. The effect will start within minutes after absorption and last up to 4 h depending on the dosage given. Till date, it is only exclusively used in animals as approved by the Food and Drug Administration. Human intoxication is uncommon, and no specific antidote is available. Naloxone, a competitive opioid receptor antagonist, was postulated to have an antidotal effect on xylazine. We report two cases of accidental human injection with xylazine. Naloxone was administered in one of the cases. Acute hypertension and mydriasis were observed; however, no apparent reversal of toxidrome was seen. This finding reveals the question regarding the efficacy and benefit of naloxone usage in xylazine intoxication. General management remains supportive of care focusing on ventilation and hemodynamics. Attending physicians should be aware of potential xylazine intoxication incidents in the area of livestock or veterinary activities.

**Keywords:**

Antidote, human intoxication, naloxone, xylazine

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**ORCID:**
*LKC: 0000-0002-6413-6658*
*AIK: 0000-0001-7791-5098*
*WMA: 0000-0002-1732-6723*
*SRS: 0000-0001-9406-6884*

**Address for correspondence:**
Dr. Lee Kee Choon, Department of Emergency and Trauma, Hospital Sultan Haji Ahmad Shah, Temerloh, Pahang, Malaysia.
E-mail: drleekeechoon@gmail.com

## Introduction

Xylazine is widely used as an animal tranquilizer to provide analgesia, sedatives, as well as muscle relaxants, to facilitate procedures on an animal. It can be administered as a single agent or in combination with other drugs through intravenous (IV), intramuscular, or peroral. However, xylazine is not approved by the Food and Drug Administration (FDA) for human use due to potential hazardous side effects. Despite that, no specific antidote is available for human xylazine intoxication, and naloxone was postulated to have an antidote effect. In this case series, naloxone was administered in one of the cases. However, no apparent reversal of toxidrome was observed, and this reveals the question regarding the usage of naloxone in xylazine intoxication.

## Case Series

### Case 1

A 28-year-old gentleman who works at a livestock farm was brought to the emergency department (ED) by his colleague after an accidental injection with cow tranquilizer over his left deltoid region. He arrived at ED 30 min after the incident in a reduced conscious state, and the drug was identified as xylazine [Figure 1]. However, the dose was unknown.



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On assessment, he was in a stuporous state and responded minimally despite vigorous external stimuli. However, airway was patent, and his breathing was normal. Blood pressure (BP) was normotensive but bradycardic with a heart rate of 38 bpm. Eye examination revealed bilateral reactive pinpoint pupils. A puncture wound with no active bleeding measuring approximately 0.5 cm × 0.5 cm [Figure 2] was seen in the left deltoid region. Otherwise, other systemic examinations are unremarkable.

Electrocardiogram (ECG) revealed sinus bradycardia with a heart rate (HR) of 44 bpm and no ST-segment changes. Arterial blood gas showed good oxygenation and normal carbon dioxide partial pressure. Blood parameters showed no evidence of acute kidney injury or liver injury. He was given 15 L/min supplemental oxygen via a nonrebreather mask and subsequently weaned down to nasal cannula. IV atropine 0.5 mg was given, and heart rate improved to 55 bpm. The Malaysia National Poison Centre was consulted for the possible antidote, and naloxone was suggested to reverse respiratory as well as central nervous system depression.

A total bolus of 1.2 mg IV naloxone was given and started on infusion as per opioid intoxication protocol. No immediate change was observed in mental status, and the vital signs remained stable. Eventually, he regained full consciousness after 24 h. Throughout admission, he did not require any inotropic or ventilatory support and was safely discharged after 48 h of observation with no neurological sequelae. Written consent approval was obtained from the patient to publish his case and images.

### Case 2

A 27-year-old male was trying to restrain an irritable cow by using a sedative agent, xylazine. However, he accidentally dropped the loaded syringe and injected himself with the drug. He was brought immediately to the ED by his coworker. On arrival at ED, he was conscious, alert, and able to give a full history of the incident. However, after 10 min, he started to become drowsy and stuporous. His airway and breathing remained normal. Subsequently, his systolic BP dropped to as low as 80 mmHg. His HR was bradycardic at the rate of 35–38 bpm, and ECG revealed sinus bradycardia. He was given a total of 2 l of 0.9% saline infusion but with no improvement in BP. Hence, noradrenaline infusion was initiated at a rate of 0.3 μg/kg/min, and his BP improved. IV atropine 0.5 mg was administered, and his HR improved to 60 bpm. He was then admitted and observed in the general medical ward. His vital signs remained stable in the ward, and he regained full consciousness with good recovery after 24 h. Written consent approval was obtained from the patient to publish his case.

## Discussion

Xylazine is a type of sedative commonly used in veterinary medicine. Its effects are due to stimulation of central alpha-2 (α2) receptor and suppression of norepinephrine release from the peripheral nerve terminal.[1] Apart from that, it is also reported to have action on cholinergic, serotogenic, H2-histamine, dopaminergic, and opioid receptors.[2]

In animals, xylazine causes hypotension, bradycardia, central nervous system depression, and respiratory depression.[3] Once administered IV, xylazine will be rapidly distributed to the animal's central nervous system and kidneys. The effect will start within minutes after absorption and last up to 4 h depending on the dosage given.[2] Previously, it was tested in both humans and animals but was subsequently banned from human use due to its potential perilous side effects. Thus far, it


**Figure 1:** Image of the drug xylazil-100 that is used by the livestock farm

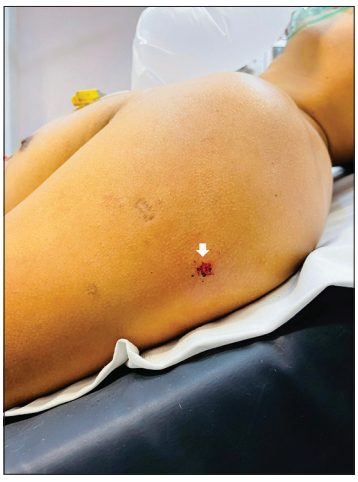

**Figure 2:** Image of the left deltoid region showed the puncture wound (white arrow) caused by accidental injection

is only exclusively used in animals as approved by the FDA.

Over the last 50 years, a total of 43 xylazine human intoxication cases were identified based on a literature review done by Ruiz *et al*. in 2014. Approximately half of the cases were due to accidental causes but nonfatal. Meanwhile, majority of fatal intoxication cases are due to consumption as an adulterant.[4] A recent forensic report in Malaysia by Teoh *et al*. has reported that there is evidence of xylazine usage in drug-spiked beverages.[5] Without proper law enforcement of this drug, this could potentially lead to an unfavorable social impact.

The general toxidrome for xylazine intoxication is summarized in Table 1.[4] Although the duration of the effect commonly lasts for a few hours, prolonged duration of up to 3 days was reported in several cases.[6] Xylazine intoxication effect can be reversed with yohimbine, tolazoline, and idazoxan.[7] However, its effectiveness as an antidote has only been tested in animals but not humans. Another drug called atipamezole which is a selective α2-antagonist is commonly used in veterinary medicine to reverse sedative and analgesic effects.[8] In a small human trial, it has shown its effectiveness in reversing α2-agonists.[9] Up to now, it is not approved for human use yet by the FDA.

### Is there a role for naloxone?

It has been postulated that administration of xylazine may stimulate the endogenous opioid release and act on mu-receptor.[10] As a competitive opioid receptor antagonist, naloxone will predictably have an antidotal effect on xylazine. Apart from that, it is suggested to use naloxone as the antidote since xylazine has a centrally acting effect similar to clonidine. However, the benefit of using naloxone in clonidine toxicity has very limited evidence with case series reporting no apparent benefit in addition to the uncertainty of correct dosage.[11] In our case, a trial bolus of 1.2 mg was administered in a divided dose, and continuous infusion is given because naloxone's duration of action is shorter than xylazine.

**Table 1: Summary of xylazine toxidrome based on system**

| Central nervous | Respiratory | Cardiovascular | Endocrine |
|---|---|---|---|
| Areflexia | Apnea | Hypotension | Hyperglycemia |
| Asthenia | Shallow breathing | Bradycardia | |
| Ataxia | | Premature ventricular contraction | |
| Blurred vision | | | |
| Disorientation | | | |
| Dizziness | | | |
| Drowsiness | | | |
| Dysarthria | | | |
| Dysmetria | | | |
| Hyporeflexia | | | |
| Miosis | | | |
| Slurred speech | | | |
| Somnolence | | | |
| Staggering | | | |
| Coma | | | |

We observed the immediate effect of naloxone in our patient whereby he developed acute hypertension and mydriasis after the drug administration. Despite that, the improvement of mental status is not obvious and rapid as expected. This finding has brought us to ponder the benefit and efficacy of naloxone usage in xylazine intoxication. Because it does not produce apparent and beneficial effects, there is a possibility of naloxone overdosage due to an increased tendency to re-bolus the drug. Eventually, this can result in severe adverse effects like acute pulmonary edema and cardiac arrhythmia.

In Case 1, IV naloxone was administered; however, the patient did not show significant improvement in consciousness level but developed adverse effects of naloxone. In Case 2, the patient was given supportive treatment with oxygen, fluids, and noradrenaline. No naloxone was administered. To date, there is no specific pharmaceutical antidote to xylazine intoxication in humans. Because there is no evidence that naloxone can reverse the effect of xylazine, one should be more cautious in administering this drug in xylazine toxicity cases. Furthermore, we observed similar outcomes in both cases. Therefore, the role of naloxone in xylazine toxicity in humans remains uncertain. More research is needed to establish the management of its poisoning in the future.

## Conclusion

General management of xylazine intoxication is mainly supportive care focusing on ventilation and hemodynamics. ED physicians should be aware of potential xylazine intoxication incidents in the area of livestock or veterinary activities. In addition, the role of naloxone remains unclear, and more research is needed to determine the safety of other antidote usages in humans.

**Author contribution statement**

Designing and coordinating the report: LKC

Literature search: LKC, AIK

Writing the review: LKC, AIK, WMWMA, SRS

All authors read and approved the final report.

**Conflicts of interest**

None Declared.

### Consent to participate
Our patient gave informed consent to use his anonymous data in scientific publications.

### Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images, and other clinical information to be reported in the journal. The patients understand that their name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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