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Prevalence of Xylazine in Umbilical Cord Tissue, October 2023-September 2024

Kari M. Midthun Ph.D., F-ABFT[1*], Alexandria A. Reinhart, Ph.D., NRCC-CC[1,2]

Abstract

In utero drug exposure is a significant public health concern for developing fetuses and neonates. Confirmation of prenatal drug exposure often relies on toxicological testing of neonatal specimens, with umbilical cord tissue (UCT) rapidly becoming the preferred matrix. Interpretation of neonatal results can be challenging when findings contain drugs commonly administered during labor and delivery, such as fentanyl, benzodiazepines, and opiates/opioids. Xylazine, a toxic adulterant increasingly found in the illicit fentanyl drug supply, can serve as a marker to differentiate between medical and illicit exposure. This study sought to determine the prevalence of xylazine in UCT testing over a 12-month period (October 1, 2023-September 30, 2024). Within one year, xylazine was reported in 2.1% (n=248) of all UCT cases positive for any drug finding and remained at consistent positive rates over the course of the 12 months (1.8-2.3% quarterly). Most samples were positive for both xylazine and fentanyl, with additional polydrug combinations commonly containing stimulants, including methamphetamine and/or cocaine. This study reports the positive detection of xylazine in neonatal UCT and highlights the need for continued study of drug trends in the neonatal population.

Keywords: Umbilical cord; Neonate; Newborn; Xylazine; Fentanyl; Pregnancy; Prenatal exposure

Introduction

In utero drug exposure is a significant public health threat to the well-being and development of the fetus and neonate. Illicit and licit use of drugs can have severe consequences on the health of the child, including both short-term and long-term effects on development and behavior [1]. While exposure and withdrawal symptoms are well characterized for some individual drug classes, such as alcohol and Fetal Alcohol Spectrum Disorders (FASD), opiates/opioids and Neonatal Abstinence Syndrome (NAS), and more recently fentanyl and Fetal Fentanyl Syndrome (FFS), the abuse of multiple drugs during pregnancy is quite common and not well understood [2,3].

To identify drug exposure in the neonatal population, health systems rely on the testing of unique neonatal matrices, such as umbilical cord tissue (UCT). This matrix possesses several advantages for identifying substance-exposed and at-risk neonates, including, but not limited to simple, non-invasive collection; universal availability with every birth; a large specimen size; and a large detection window encompassing roughly the last trimester of pregnancy [4]. In general, commercial testing scopes have focused on more traditional drugs of misuse and commonly abused prescription medications.

Affiliation:
[1]NMS Labs, Horsham, Pennsylvania, USA
[2]Dr. Reinhart's present address: Ambler, Pennsylvania, USA

***Corresponding author:**
Kari M. Midthun, NMS Labs, Horsham, Pennsylvania, USA.

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Table 1: Summary of UCT Xylazine and Fentanyl Positivity from October 2023-September 2024.

	TOTAL SAMPLES TESTED					XYLAZINE-POSITIVE CASES			
	Samples Screened	Confirmed Positive (%)	Xylazine Positive (%)	Fentanyl Positive (%)	Norfentanyl Positive (%)	Total Positive Xylazine	Xylazine + Fentanyl (%)	Xylazine + Norfentanyl (%)	Xylazine only (%)
Oct to Dec 2023	6259	2702 (43)	56 (2.3)	212 (7.8)	254 (9.4)	56	55 (98)	55 (98)	0 (0.0)
Jan to Mar 2024	6704	2890 (43)	56 (1.8)	193 (6.7)	223 (7.7)	56	55 (98)	55 (98)	1 (1.8)
Apr to Jun 2024	6542	2731 (41)	61 (2.3)	195(7.1)	240 (8.8)	61	58 (95)	57 (93)	1 (1.5)
Jul to Sept 2024	7428	3069 (41)	75 (2.3)	195 (6.4)	237 (7.7)	75	71 (94)	72 (97)	0 (0.0)
TOTAL (%)	**26933**	**11392 (42)**	**248 (2.1)**	**795 (6.9)**	**954 (8.3)**	**248**	**239 (96)**	**239 (96)**	**2 (0.80)**

As is true of other neonatal matrices, interpretation of UCT results can be complicated by iatrogenic administration of drugs. Benzodiazepines, opiates/opioids, and fentanyl are commonly administered during labor and delivery care. While not detected in every birth, labor and delivery administered drug UCT findings have been reported [5-7]. Thus, careful consideration of both the UCT toxicological findings and the medical history of the mother and child are required when interpreting results.

In 2022, the Drug Enforcement Agency (DEA) issued a report about the growing threat of xylazine and its mixture with illicit drugs [8]. Xylazine, a sedative analgesic authorized solely for veterinary use in the United States, is being reported as a common adulterating agent in illicit drug mixtures. While most frequently seen in combination with fentanyl, xylazine has also been detected in seized drug mixtures containing cocaine, heroin, and other substances [9]. These findings have been corroborated with forensic testing, where increases in the presence of xylazine in postmortem and driving under the influence of drug(s) related casework have been occurring since 2019 [10]. In terms of interpretation, the detection of xylazine as a toxicological finding serves as a biomarker for substance abuse and/or misuse. Furthermore, its presence can be used to help differentiate between licit and illicit exposure to medically significant findings, including fentanyl and opiates/opioids.

Though recent focus has been given to understanding the potential adverse health effects of xylazine due to its presence in illicit drug supplies [11,12], the effects of illicit drug adulterants and cutting agents have not been well studied in humans, particularly when found in combination with other drugs. Thus, little is known about the risks of pediatric exposure to xylazine beyond case reports in children [13], with research into fetal exposure remaining in its infancy [14]. In early 2023, Midthun et al. [15] reported the ability to detect xylazine and other adulterating agents in UCT samples that had previously tested positive for opiates and/or cocaine [15]. Of note from the study, xylazine was only detected in cases which were positive for opiates. By the end of 2023, several commercial laboratories began offering testing for xylazine in UCT.

Here, we report the prevalence of xylazine in a large population of UCT samples submitted for routine toxicological analysis over a 1-year period. The occurrence of fentanyl in combination with xylazine was also determined, as well as common drug combinations with xylazine-positive samples. While more studies are needed to better characterize multi-drug prenatal exposure and its impacts on the health and well-being of the neonate and family, the ability to detect and identify these substances via toxicological testing is an important first step in treatment and monitoring.

Methods

Data were extracted from NMS Labs' (Horsham, PA) laboratory information management system and were analyzed to characterize xylazine-positivity in UCT samples submitted for clinical analysis. A liquid chromatography-tandem mass spectrometry (LC-MS/MS) method for analyzing xylazine in UCT was developed and fully validated according to qualitative guidelines from ANSI/ASB Standard 036, Standard Practices for Method Validation in Forensic Toxicology [16]. All UCT samples, which underwent comprehensive drug testing from 1 October 2023 to 30 September 2024, were included.

Briefly, UCT samples were received as cleaned, weighed pieces of tissue. Following addition of a deuterated internal standard and organic solvent, samples were homogenized and then centrifuged prior to analysis of the supernatant. The cutoff calibrator concentration for xylazine via LC-MS/MS screening was 0.5 ng/g tissue, with duplicate calibrator control samples being used to determine point-to-point calibration on each analytical run. Any case sample that

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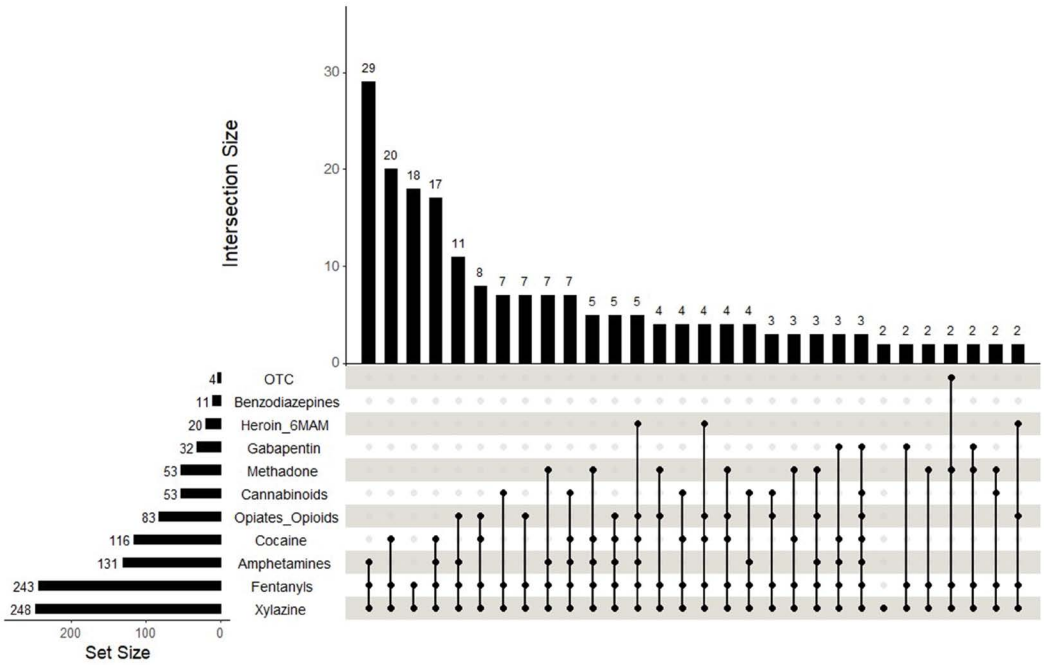
calculated to greater than the cutoff calibrator, a presumptive positive result, was then confirmed by a separate LC-MS/MS method with a xylazine reporting limit of 0.5 ng/g tissue.

Statistical analyses were performed using Microsoft Office® and RStudio® (RStudio Team (2022). RStudio: Integrated Development for R. RStudio, PBC, Boston, MA. URL http://www.rstudio.com/).

Results

From 1 October 2023 to 30 September 2024, the number of UCT samples which screened and confirmed positive for xylazine remained stable without any significant statistical differences ($P > 0.05$). The overall sample positivity rate ranged from 41-43% (Table 1, n = 26933). All UCT samples containing xylazine (n = 248), fentanyl (n = 795), and/or norfentanyl (n = 954) also remained stable without any significant statistical differences ($P > 0.05$). From samples reported with at least one positive finding, xylazine positivity ranged from 1.8-2.3%, fentanyl positivity ranged from 6.4-7.8%, and norfentanyl positivity ranged from 7.7-9.4%. As shown in Table 1, xylazine samples were nearly always found in combination with fentanyl (94-98%) and/or norfentanyl (93-98%). Of the 248 xylazine-positive samples identified, 5 samples were reported without concurrent findings of either fentanyl or norfentanyl (data not shown). Of these, only 2 UCT samples were reported with xylazine being the sole finding; the remaining samples were positive for other drug findings, including methamphetamine and cocaine. Seven xylazine-positive samples contained either fentanyl or norfentanyl, but not both compounds.

The xylazine-positive data was further evaluated to look for polydrug combinations across a broader scope of drugs and drug classes, including both illicit and prescription drugs (Figure 1). Sample findings were tabulated based on drug class positivity, with category labels encompassing parent and metabolite compounds and/or related drugs. For example, the drug class Amphetamines included both amphetamine and methamphetamine, as well as 3,4-methylenedioxymethamphetamine (MDMA). Benzodiazepines included alprazolam, diazepam, nordiazepam, clonazepam, 7-amino clonazepam, and lorazepam. The class Opiates_Opioids included morphine, hydromorphone, codeine, hydrocodone, norhydrocodone, oxycodone, noroxycodone, tramadol, and O-desmethyltramadol. Fentanyls included fentanyl, acetyl fentanyl, and norfentanyl. Other drug class categories included Cocaine (with cocaethylene and benzoylecgonine), Methadone (with metabolite 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP)), Cannabinoids (delta-9-tetrahydrocannabinol (THC) and delta-9-carboxy THC), Gabapentin, Heroin (indicated by the presence of 6-monoacetylmorphine (6MAM)), and Over-the-Counter (OTC, here identifying dextro/levo-methorphan) medications.



UpSet plot characterizing xylazine-positive UCT samples (n=248) and corresponding polydrug findings from October 2023-September 2024. The bar graph (set size) on the left represents the frequency of a drug class finding. The dot diagram with connecting lines shows the frequency of polydrug combinations, or intersections, between various drug classes, with a single dot representing a single drug class finding. The frequency of each drug combination is shown by the histogram at the top of the plot. OTC: over-the-counter, 6MAM: 6-monoacetylmorphine.

Figure 1: UCT Xylazine Co-Positivity from October 2023-September 2024.

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While xylazine and fentanyl are commonly found together, they are seldom reported as the only drug findings in xylazine-positive UCT samples (Figure 1). The most common UCT polydrug combination encountered in this study involved findings of xylazine and fentanyl with stimulants, including amphetamines (n=29), cocaine (n=20), or a mixture of both (n=17). These combinations were followed by mixtures with opiates/opioids, cannabinoids, and methadone. Heroin made up the smallest share of polydrug combinations that included an illicit substance in xylazine-positive samples. Benzodiazepines were also detected in 11 samples, though these findings varied significantly in polydrug combinations (data not shown).

Discussion

Over the past several years, xylazine has been a growing concern as an adulterant in illicit drug supplies, with its impacts on adult populations being noted heavily in the media. However, xylazine must also be recognized as having impacts on the pediatric population and be a cause of concern for pediatric exposure [13]. UCT testing is one method to identify *in utero* drug exposure and identify infants who may be from at-risk environments. In this study, the prevalence of xylazine consistently ranged from 1.8-2.3% of reported positive UCT samples, but there was an overall decrease in sample positivity for any drug from 43% to 41%. Additionally, most samples positive for xylazine were positive for multiple drugs/drug classes, many of which were illicit, thus highlighting the likelihood of misuse.

It is important to note that drugs commonly administered during labor and delivery, such as fentanyl, benzodiazepines, and opiates/opioids, can cross the placental membrane and may be present in UCT findings. Caution must be taken to avoid mislabeling all UCT drug findings as illicit use. The presence of illicit drugs and adulterating agents, such as xylazine, can be used to help differentiate medical administration from illicit street use, particularly in the case of fentanyl findings.

In general, studies on prenatal drug exposure are few and limited in scope. The studies that are available often rely on self-disclosure of maternal drug use during pregnancy, which can be unreliable, and/or testing of maternal/neonatal specimens to indicate *in utero* exposure. Thus, there is an overall lack of information concerning the frequency of prenatal drug use and its impact(s) on the newborn. Identifying these situations are critical to ensure that proper health care is given to the neonate, that services are provided to the parents or guardians who care for the neonate, and that long-term monitoring and follow-up care is available.

Conclusion

Drug exposure in the neonatal population is a growing public health concern. While testing of neonatal specimens assists in identifying prenatal exposure, interpretation can be complicated by medical administration of drugs, such as fentanyl and opiates/opioids. The inclusion of xylazine into UCT test scopes serves as an important biomarker to help differentiate between illicit and iatrogenic exposure. Over a 12-month period, 248 UCT specimens (2.1%) reported positive for the presence of xylazine, and nearly all samples being found in combination with other drugs. Documentation of UCT drug presence, including xylazine, over time will help to better characterize prenatal drug exposure trends, short-term and long-term impacts on neonatal and infant populations, and the need for support for families impacted by prenatal drug use.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The data derived in this article were accessed from NMS Labs. The data will be shared upon reasonable request to the corresponding author.

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