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Toxic Adulterants Found in Umbilical Cord Tissue (UCT)

Toxic Adulterant Alert

Substance abuse treatment providers, clinicians, outreach workers, and public health agencies should be aware of the following information. *In utero* drug exposure is a significant public health threat to the well-being and normal development of the neonate. Recently, testing of umbilical cord tissue (UCT) has been employed to measure illicit drug exposure. UCT testing is a well-established method which uses a segment of the newborn's cord collected at the time of delivery. UCT shares a detection window similar to that of meconium, as drugs consumed by the mother during the third trimester may be retained. The *in utero* effects of illicit drug adulterants and cutting agents have not been well studied in humans, nor has their presence been demonstrated to be an effective means for assessing adverse health effects in the neonate.

Background:

Inactive cutting agents and pharmacologically active adulterants are added to the street drug supply to increase the number of doses that can be sold from a given amount of active illicit drug. The most common adulterating agents include dietary staples (e.g., caffeine), current therapeutics (e.g., lidocaine, acetaminophen, and diphenhydramine), and xenobiotic compounds attributed to illicit drug use origins (e.g., levamisole, phenacetin, metamizole (dipyrone), and xylazine). A 2018 Danish study analyzed the blood of more than 400 first-trimester pregnant women and reported ~18% of participants testing positive for prescription and/or OTC compounds, such as antidepressants or acetaminophen, respectively. Illegal drugs were found in 0.9% of subjects, with common cocaine adulterants (levamisole and phenacetin) also identified. Subsequently, a study from Mexico has shown the ability to analyze maternal hair samples and detect licit and illicit drug consumption during pregnancy, including antihistamines, cocaine, ketamine, and novel psychoactive substances. Despite efforts to understand maternal xenobiotic consumption, very little is known about the risks of fetal exposure to these toxic, adulterating substances.

UCT and Drug Exposure:

Recently, a U.S. study analyzed 300 cocaine- or opiates-positive UCT samples for the presence of more than 20 common drug adulterating/cutting substances. More than 97% of the UCT samples analyzed were positive for one or more of these compounds. While caffeine and lidocaine were the two most common, many of the UCT samples contained adulterants of illicit origin, as summarized in Table 1. Little is known about the impacts and adverse effects of adulterating compounds on the fetus/neonate, particularly when consumption exceeds dietary and therapeutic recommendations and/or when these compounds are combined with other illicit drugs. However, drugs and adulterants that suppress the immune system (e.g., deplete white blood cells) are a significant threat to neonates and children. This study highlights the need for future research on this topic.

Table 1. Positivity of Illicit Origin Adulterants in Umbilical Cord Tissue (UCT)

Illicit Adulterating Compound	Positivity in Total Cohort (% Total Patients)	Positivity in Cocaine Subgroup (% Cocaine Patients)	Positivity in Opiates Subgroup (% Opiates Patients)
Levamisole	35 (12%)	32 (18%)	3 (3%)
Phenacetin	15 (5%)	9 (5%)	6 (5%)
4-Methylaminoantipyrine*	3 (1%)	0 (0%)	3 (3%)
4-Formylaminoantipyrine*	2 (0.7%)	1 (0.5%)	1 (0.9%)
4-Aminoantipyrine*	1 (0.3%)	0 (0%)	1 (0.9%)
Aminopyrine*	1 (0.3%)	0 (0%)	1 (0.9%)
Xylazine	3 (1%)	0 (0%)	3 (3%)
Total Patients	300	183	117

Adulterant positivity expressed as totals and percentages (%) of patients in the total cohort, cocaine-positive subgroup, and opiates-positive subgroup, respectively. (Table modified from Midthun *et al.,* 2023) Asterisks (*) indicate metabolites of metamizole (dipyrone).

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The opinions, findings, recommendations, and conclusions expressed in this publication are those of the authors and do not necessarily reflect those of the U.S. Department of State. More information on the presence of adulterants in UCT is available by contacting kari.midthun@nmslabs.com .

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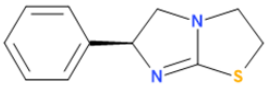
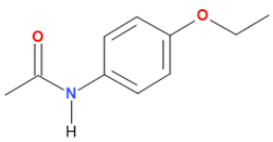
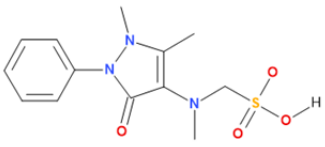
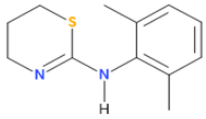
The Center for Forensic Science Research & Education

Health Effects

Adulterants of Illicit Origin	Drug Facts	Known Adverse Facts
Levamisole 	• Antihelminthic (veterinary use) • Withdrawn from pharmaceutical markets due to adverse side effects in 2000 (U.S.) and 2003 (Canada)	• Acute &/or Prolonged: Nausea, diarrhea, dizziness, muscle pain, headache, fever, insomnia, convulsions, neutropenia, agranulocytosis, methemoglobinemia • Unique Manifestations: Purpura retiform, systemic vasculitis, cutaneous necrosis, intravascular thrombosis • Pediatric Case Report: 7-yo in France presented to ED with dizziness, convulsions, abdominal pain, and vomiting
Phenacetin 	• Pain reliever, antipyretic • Metabolized to acetaminophen • Banned by FDA in 1983 due to concerns over carcinogenesis, nephropathy, methemoglobinemia, and hemolytic anemia	• Acute: Headache, nausea, shortness of breath, methemoglobinemia, ataxia, lethargy, confusion • Unique Manifestations: Nephropathy, hemolytic anemia, kidney and bladder cancer
Metamizole (Dipyrone) 	• Analgesic, antipyretic • Banned by FDA due to reports of agranulocytosis in 1977 (dipyrone) and 1979 (metamizole) • Multiple metabolites (Table 1*), some are active	• Acute: Gastrointestinal bleed, headache, dizziness • Unique Manifestations: Renal dysfunction, hypersensitivity, severe to fatal agranulocytosis • Pediatric Case Report: 4-yo in Turkey developed life-threatening agranulocytosis and anemia
Xylazine 	• Analgesic (veterinary use) • Does not respond to opioid reversal agents (e.g., naloxone)	• Acute: CNS depression, sedation, bradycardia, orthostatic hypotension, miosis • Unique Manifestations: CNS depression, skin lesions, may potentiate sedation and respiratory depression when combined with other illicit drugs • Pediatric Case Report: Attempted DFSA of 4-yo in Germany; collapsed and became unconscious

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