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EDITED BY
Marco Fiore,
Università degli Studi della Campania "Luigi Vanvitelli", Italy

REVIEWED BY
Etrusca Brogi,
University of Pisa, Italy
Juan Carlos Lopez-Delgado,
Hospital Clinic of Barcelona, Spain

*CORRESPONDENCE
Richard M. Pino
✉ rpino1@lsuhsc.edu

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Diagnosis and management of the patient with contaminated illicit drug poisoning

Richard M. Pino[1]* and Patrick R. McGrew[2]

[1]Department of Anesthesiology, Louisiana State University Health Sciences Center, New Orleans, LA, United States, [2]Department of Surgery, Tulane University School of Medicine, New Orleans, LA, United States

The diagnosis and management of poisoning is essential in critical care medicine. Traditionally, these conditions fall under the category of toxidromes that are the signs and symptoms associated with a particular class of poisons. However, there has been a steady increase in designer drugs and contaminants of recreational drugs themselves. Examples of adulterants in cocaine include the local anesthetic benzocaine and the anti-parasitic levamisole. This paper presents the clinical signs, laboratory findings, and treatment of patients who have been exposed to these substances.

KEYWORDS

adulterants, cocaine, toxicity, cathinones, cannabis, illicit drugs, xylazine

1. Introduction

Admissions to the ICU related to substance abuse is, unfortunately, a common global issue. A recent study revealed that substance abuse was responsible for one quarter of ICU admissions and 23% of total charges (1). Illicit drug use was associated with 13% of these patients (1). Identification of the illicit drug on clinical presentation is often difficult. These substances often fall into multiple categories of toxidromes, the signs and symptoms associated with a particular class of poisons (2). Polysubstance abuse is common.

There has been the increasing use of "adulterants" that are legal substances which are added to these illicit drugs. This process, called "cutting", is to either further enhance their effects or expand volume, both of which enhance the drug dealers' profits (3, 4). Laboratory tests can confirm the most common illicit substances but often will not identify altered forms (5).

Our experience in a trauma center encompasses patients with substance abuse issues, but we had sparse knowledge of contaminants before caring for the patient in the clinical example below. In this paper we present examples illicit drug contaminants, a little-known subject for critical care physicians.

1.1. Cocaine

Cocaine is one of the most common illegal psychostimulant drugs (4, 6, 7). It is abused as either the water-soluble hydrochloride salt or a water-insoluble base known as "freebase and crack". Cocaine blocks the transporters for dopamine, norepinephrine, and serotonin (8). With this blockade, there is continued stimulation by monoamines at the pre- and post- synapses to create euphoria that leads to addiction. Symptoms include tachycardia, hypertension, hyperthermia, and agitation (7). The long list of sequelae includes myocardial and cerebral infarctions. Acute kidney injury may be related to decreased renal blood flow from vascular smooth muscle constriction and rhabdomyolysis (9).

Cutaneous vasculopathy with rheumatologic features including antineutrophil cytoplasmic antibodies (ANCA) can occur (10).

Adulterants in seized cocaine samples include levamisole, phenacetin, lidocaine, imidazole, and caffeine (11–13). Each of these compounds themselves will cause pathologic changes like cocaine making additional diagnoses difficult (Table 1).

Levamisole is an antihelminthic in widespread veterinary use. It had been used as an adjuvant chemotherapy agent but was withdrawn from the US market in 2000 after side effects of agranulocytosis, cutaneous vasculopathy, and leukoencephalopathy were identified (14–16). Levamisole is the most widely used adulterant in up to 88% of cocaine samples to improve its euphoric effects (4, 14, 15). The mechanism for euphoria includes the metabolism to aminorex, an amphetamine-like substance once used as a diet drug. Aminorex was taken off the market secondary to pulmonary hypertension (17). Levamisole increases antibody production to various antigens by functioning as a hapten involved with isoimmune antineutrophil cell membrane antigens. Cutaneous manifestations include purpura, hemorrhagic bullae, and livedo reticularis (10). An immune-mediated mechanism has been suggested for eosinophilic inflammatory coronary artery pathology (18).

Local anesthetics are added to cocaine since they have the same analgesic properties and cannot be detected as an adulterant by the drug user. Physicians are familiar with lidocaine used as an antidysrhythmic and local anesthetic controlled by the FDA and in the over-the-counter topical analgesics. What is likely unknown is that 99.9% pure lidocaine and benzocaine powders can be purchased for "research and development" from common online sites without a prescription. The established maximum cumulative dose of intravenous lidocaine during treatment of ventricular dysrhythmias is 3 mg/kg (19). As a local anesthetic injection without epinephrine the maximum dose is 4.5 mg/kg (20). Clearly the drug dealers cutting cocaine with lidocaine greatly exceed this maximum. Overdose results in negative inotropy, vasodilatation, seizures, and respiratory depression (20). Hypercapnia and respiratory acidosis exacerbate central nervous system depression. A report from the United Kingdom indicated that 60% of cocaine was adulterated with benzocaine (21). Benzocaine is rapidly absorbed across mucous membranes. Methemoglobinema results from the oxidation of the iron in hemoglobin to the ferric state. Cyanosis will be manifested after topical 150–300 mg, concentrations of methemoglobin result in metabolic acidosis, convulsions, and coma; levels about 70% are lethal (21).

Caffeine is the most widely used stimulant consumed by over 80% of the population in the world. In moderate amounts of less than 400 mg/day in healthy adults there is nominal toxicity (22). Toxic symptoms occur after injection of 1 gram, hospitalization is needed after 2 g, and ingested doses of 5–50 g are fatal (23). It undergoes acetylation, oxidation, and N-demethylation in the liver (6). Therefore, alcohol and abused drugs in addition to cocaine potentiate the effects of caffeine. Caffeine enhances the reinforcing effects of cocaine and its motivational value (24). The combination of caffeine and cocaine makes users more likely to keep seeking out the drug than they would if they were addicted to cocaine alone.

Phenacetin is an antipyretic and analgesic that is cleaved to form acetaminophen. It was removed from the market because of renal carcinogenicity. It is a negative inotrope, can generate methemoglobinemia through its metabolites, and can cause hemolytic anemia (25–27). Phenacetin has no stimulant properties but is used as a cutting agent to increase the bulk of cocaine.

Imidazole has fungicidal, antiprotozoal, and antihypertensive properties (26). The most common use is as a topic antifungal such as ketoconazole. It is part of the theophylline molecule derived from tea leaves and coffee beans and acts as a central nervous system stimulant. Imidazole itself is hepatotoxic via ATP depletion in cells with mitochondrial damage.

TABLE 1 Acute effects of cocaine and cannabis contaminants.

Illegal drug	Contaminant	Acute effects
Cocaine	Levamisole	Pulmonary HTN Agranulocytosis Cutaneous vasculopathy Negative inotropy
	Lidocaine	Respiratory depression Seizures Vasodilatation
	Phenacetin	Negative inotropy Hemolytic anemia Methemoglobinemia
	Imidazole	Hepatotoxicity
	H	Seizures Cardiac dysrhythmias hyperventilation
	Benzocaine	Methemoglobinemia
Cannabis (inhaled)	Vitamin E and pine rosin	Diffuse alveolar damage Bronchiolitis Organizing pneumonia Pneumonitis
	Brodifacoum	Bleeding

1.2. Cannabis

Cannabis is the most widely used psychoactive substance. Through Δ^9 -tetrahydrocannabinol (THC), cannabinoid receptors CB_1 in central and peripheral neurons are stimulated. Usually, the effects of decreased locomotor activity, cognitive impairment, analgesia, hypothermia, and appetite stimulation are considered of low toxicity but may be exacerbated when consumed in large doses (28, 29).

Cannabis can also be smoked using E-cigarettes containing Δ^8 -tetrahydrocannabinol synthesized from cannabidiol (CBD) (30, 31). Cutting agents in high levels, in addition to heavy metals leaching from the devices, are respiratory irritants (Table 1). Vitamin E acetate is a cutting agent that has been added to marijuana oils and has been associated to vaping-associated lung injury (EVALI) that includes diffuse alveolar damage, bronchiolitis with organizing pneumonia, and granulomatous pneumonitis (32). Pine rosin, a known lung irritant has been identified as an adulterant (31). Lung examination upon presentation does not correlate with the severity of the disease that can include diffuse alveolar damage, pneumonitis, and organizing pneumonia (30).

Synthesized cannabinols are dissolved in alcohol and acetone and sprayed on plant material. These are sold under a variety of names such as "K2" and "Spice". They are classified as DEA Schedule 1 but compositions are continually modified to circumvent this DEA classification. Intoxication can be severe including psychosis, respiratory depression, cardiac arrest, nephrotoxity, hyperemesis, rhabdomyolysis, hyperthermia, seizures, and cerebral ischemia (33). The most lethal adulterant of synthetic cannabinoids is brodifacoum, a vitamin K-dependent antagonist (34, 35). It is used to enhance the effects because of longer periods of lipid storage, hepatic metabolism, and slow release. Compared to the anticoagulation of warfarin it is 100 times greater and has a longer half-life of 20–130 days (35).

1.3. Synthetic cathinones

Synthetic cathinones are a group of potent designer drugs, often referred to as "bath salts". Their effect is like 3,4-methylenedioxymethamphetamine (MDMA; ecstasy) with the blockade of dopamine and norepinephrine uptake (36). Animal studies demonstrated that the synthetic cathinone methylenedioxypyrovalerone (MDPV) has greater potency than cocaine with respect to hyperactivity and cardiovascular stimulation (36). Neurologic symptoms include agitation, paranoia, hallucinations, myoclonus, and psychosis. In addition to hyperthermia, hypertension, and tachycardia liver failure, kidney failure, and compartment syndrome with rhabdomyolysis have been reported (37).

1.4. Xylazine

Xylazine is a veterinary drug used as a sedative, analgesic, and muscle relaxant (38, 39). It has a structure that is similar to phenothiazines, tricyclic antidepressants, and clonidine. As for clonidine, it is a potent central α_2-receptor agonist that will decrease the release of norepinephrine and dopamine. The intended use, in addition to cutting, is to enhance the sedation and analgesia of the illicit drug. Xylazine was first identified as a cutting agent in Puerto Rico and has adulterated heroin and cocaine and (38, 39). The contaminant of fentanyl with xylazine has been considered as the deadliest drug threat in the United States (40). More than 90% of illicit drug samples in Philadelphia are positive for xylazine with the street names "tranq", "tranq dope", and "zombie drug" (41).

The most noted side effect of xylazine is characteristic necrotic skin ulcers that are likely caused by vasoconstriction and poor skin perfusion (42). Based on case reports, the effects of overdosage include hypotension, bradycardia, hyperglycemia, areflexia, elevated cardiac enzymes, coma, and respiratory failure (43).

2. Management of complications

The acuity of substance abuse patients admitted to the ICU is complex but well within the realm of care addressed by intensive care physicians.

Respiratory embarrassment may be related to the overdose suppression of spontaneous ventilation or pulmonary parenchymal pathology as found with EVALI. The need for tracheal intubation and mechanical ventilation is straight-forward for most of these patients and often performed before the patient arrives in the ICU. Systemic glucocorticoid therapy was shown to be effective in the treatment of EVALI (32).

As many of the patients are polysubstance abusers, treatment of the drug effects, as well as underlying **psychiatric issues**, may require the use of multiple agents such as quetiapine and benzodiazepines (33, 44). For severe withdrawal, high dose lorazepam alone was ineffective when compared to the synergistic actions of propofol infusions with reduced lorazepam doses (45).

Acute kidney injury treatment is largely supportive (9). Restoration intravascular volume is essential since acute tubular necrosis may be related to hypovolemia resulting from poor intake, diarrhea, and vomiting. The latter is often associated with altered electrolyte levels. CPK's should be monitored to reveal rhabdomyolysis that may not be evident on physical examination. Dialysis may be necessary (9).

Cardiovascular toxicity, especially with cocaine, is the most difficult life-threatening processes requiring ICU care. The evidence for pharmacologic treatment is limited for the management of tachycardia, hypertension, dysrhythmia, and coronary vasospasm in a comprehensive review of the literature (46). Labetalol and carvedilol will control hypertension and tachycardia. Nitroglycerin is recommended for cocaine-associated chest pain and vasospasm with the risk of tachycardia (47). Dexmedetomidine will control hypertension at high doses (1.0 μg/kg) with the possibility of bradycardia (48). Beta blockers will decrease heart rate as expected but are used cautiously to prevent unopposed hypertension. Esmolol is effective but will cause more hypotension when comparted to other beta blockers. The sequelae of hypertension and tachycardia related to hypoxemia from methemoglobinemia require treatment especially for patients with cardiovascular disease or levels of ≥30% by co-oximetry (25, 49). Methylene blue (1%, 1–2 mg/kg) over 5 min with repeat every 30 min is the usual therapy. Hyperbaric oxygen treat has been reported for methemoglobinemia that was refractive to methylene blue. The cardiac effects of caffeine overdose are ameliorated with dialysis.

The extensive **skin necrosis** and infection related to xylazine is treated with appropriate antibiotics, topical treatment, and surgical debridement if needed.

3. Take home message

The management of patients requiring ICU care for toxicities related to substance abuse is challenging. The clinical pathophysiology may be related to a single drug, multiple drugs, and often adulterated illegal agents. For many of these patients, such as the one described above, supportive critical care is an easily identifiable task but comes with the cost of extensive resource management. It is critical to consider adulterants that would cause unexpected findings such as methemoglobinemia, lidocaine toxicity, necrotic skin lesions, or rhabdomyolysis in the absence of trauma or a compartment syndrome.

Author contributions

PM and RP equally contributed to the research, writing, and editing of this manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The author RP declared that he was an editorial board member of Frontiers at the time of submission. This had no impact on the peer review process and the final decision. The authors declared that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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