

Toxicology News

September 2009

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New Cocaine Cutting Agent Poses Greater Risk to Users

By Donald F. LeGatt

Cocaine is a potent, naturally occurring central nervous system stimulant derived from the plant *Erythroxylon coca*. When self-administered by drug abusers, it is usually taken by nasal insufflation (hydrochloride) or intravenous injection (base). Cocaine has also been used therapeutically, although rarely, as a local anesthetic in ear, nose, and throat surgery. Commercial topical preparations (40 and 100 mg/mL) are available in Canada (www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon) and the United States (www.rxlist.com).

Cocaine destined for the drug abuse scene is often deliberately diluted with other substances at some stage of production, packaging, or distribution to increase the apparent quantity (using substances such as salt, lactose, starch, ascorbic acid, and sucrose); to provide an effect similar or complementary to that of the cocaine (procaine, benzocaine, or tetracaine); or to attenuate cocaine's side effects (diltiazem or hydroxyzine) (1, 2).

Levamisole detected

In September 2005, the clinical toxicology laboratories at the University of Alberta Hospital and the medical laboratory DynaLIFE_{DX}, both in Edmonton, first reported detecting an "unusual" drug with cocaine and its metabolites in urine specimens submitted for testing, namely levamisole (3) (Figure 1). The drug was identified using routine gas chromatography/mass spectrometry (GC/MS) confirmation procedures: liquid/liquid extraction followed by GC/MS analysis in total ion scan mode.

The researchers confirmed the presence of levamisole in urine extracts by comparison to a reference compound, based on a retention time match of ± 0.15 minutes and a mass spectrum match (probability-based quality match > 0.60 and a m/z

match of 3 to 5 major ions between unknown and reference standard). Levamisole is the L-isomer of the racemate, tetramisole; the GC/MS analysis performed did not appreciate.

Around the same time, the Health Canada Drug Analysis Service Laboratory in Longueuil, Quebec, analyzed a representative sample from a Columbian cocaine shipment seized in Montreal that had been destined for Alberta. The sample also contained levamisole in combination with cocaine. The cocaine-levamisole combination has been reported by other investigators in urine specimens (4) and seized cocaine shipments (5).

Deworming agent

Levamisole is a veterinary deworming agent once used as an immunomodulator for treatment of rheumatoid arthritis and colorectal cancer in humans. Discontinued for both human and veterinary applications in Canada in 2005, the drug is still used for veterinary purposes in the United States and South America, where it is sold under brand names such as Big L Pour-On for Cattle and Big L Wormer for Poultry & Pigs. Levamisole can be purchased in bulk on the Internet, for example, from Changzhou Animal Health Products, with a minimum order of one metric ton.

The use of levamisole as a cocaine cutting agent has been steadily increasing. Levamisole was grouped in the "other" category by the Special Testing and Research Laboratory of the U.S. Drug Enforcement Administration, a category that accounted for 11% of all seizures in January 2007. In April 2009, levamisole was found in 57% of seizures, and is now the most prominent cutting agent (2). Figure

Continued on page 6

Inside...

Designer Drugs Pose Challenge	2
Federal Testing Changes Coming.....	4

Case Study: Designer Drugs Pose Diagnostic Challenge

By Christina Murray, Vito J. Rocco, and John Wilson

Initial history and presentation

In January 2006, a 16-year-old male presented to the emergency department in a suburb of Detroit with agitation, aggressive behavior, paranoia, and intense suicidal ideation after taking a drug he had purchased off the Internet. "Give me a gun, I want to kill myself," the patient had repeated. The patient reported he had ingested a drug he thought was "2C-I," a designer drug with hallucinogenic effects.

On arrival at the hospital, the patient was disoriented and agitated with a Glasgow Coma Score (GCS) of 13. His vital signs on arrival demonstrated sinus tachycardia (123 beats/min) and tachypnea (28 breaths/min). He was afebrile and normotensive. Pertinent findings on physical examination included dry mucous membranes, tachycardia, and dilated pupils (7 mm bilaterally). The patient had a medical history significant for bipolar disorder and depression, with a prior suicide attempt. He had been off his prescribed medications, Effexor and Seroquel, for approximately one year.

Investigations

Initial screening was negative for alcohol, acetaminophen, and salicylate. The basic metabolic panel was unremarkable except for mild hyperglycemia (173 mg/dL). The complete blood count was significant for leukocytosis (19.0 bil/L), elevated hemoglobin (17.6 g/dL), and elevated hematocrit (51.3%). A CT scan of the brain was negative for any acute intracranial process. An ECG showed a sinus arrhythmia, but was otherwise unremarkable. Further comprehensive toxicological analysis was positive for 4-iodo-2,5-dimethoxyamphetamine (DOI).

Management

The patient required multiple doses of Ativan (an anxiolytic) and Haldol (an antipsychotic) as well as physical restraints to calm him down in the emergency department. He was admitted to the pediatric floor for further cardiac monitoring. A social worker and a pediatric psychiatrist evaluated him. He was later discharged home in stable condition with recommendations for psychiatric follow-up.

Background

Designer drugs are synthetically derived analogs of commonly abused and federally controlled substances, with amphetamine analogs being among the most popular (1). Designer drugs were so named be-

cause they were chemically designed to evade the law before the Controlled Substances Act was revised to include them. They are synthesized by altering the chemical structure of amphetamine by attaching various substituents to different positions on the phenyl ring or carbon side chain. One of the most widely used amphetamine analogs is methylenedioxymethamphetamine (MDMA), which has many street names, including ecstasy and X (1).

The patient in this case thought he had ingested the designer drug known as 2C-I, but in reality ingested the much more potent and longer-acting hallucinogen DOI. The drugs 4-iodo-2,5-dimethoxyphenethylamine (2C-I) and DOI are both psychedelic amphetamine analogs (Figure 1) (2, 3). Although less readily available on the street than MDMA, these drugs can be purchased via the Internet. Internet sites offer a plethora of information on not only how to obtain but also how to synthesize and ingest hallucinogens (5).

DOI belongs to a class of hallucinogens known as phenylalkylamines. Phenylalkylamines can be subdivided into phenylethylamines (which include mescaline) and 1-phenylisopropylamines (which include amphetamine) (4). Classical hallucinogens are structurally similar to several naturally occurring neurotransmitters, including serotonin, norepinephrine, epinephrine, and dopamine. However, serotonin (5-HT) is the only neurotransmitter that has consistently demonstrated involvement in the mechanism of action of hallucinogens.

Phenylisopropylamine hallucinogens such as DOI bind selectively to 5-HT₂ receptors (4, 8, 9). This receptor type is found in high concentrations in the cortical and limbic regions (6). Although the evidence points to 5-HT_{2A} as being the primary site mediating the effects of phenethylamine hallucinogens, other subtypes are thought to play a modulatory role (8). DOI is metabolized primarily by O-demethylation and has inhibitory effects on the cytochrome P450 isoenzyme CYP2D6 (2).

Discussion

The compounds that make up the hallucinogen class of drugs have different structures, mechanisms

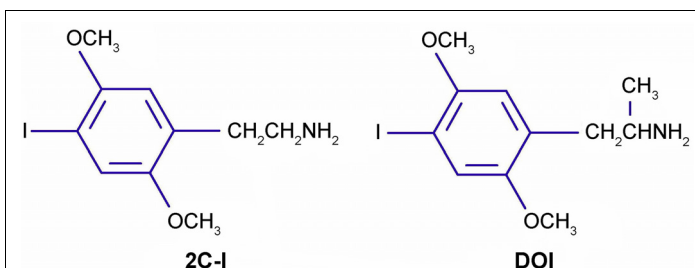


Figure 1. Chemical Structures of 2C-I and DOI

of action, and side effects. With the exception of LSD, and possibly PCP, most of these drugs do not produce actual hallucinations but instead cause psychosis, paranoia, and delusions. Serotonin-like agents alter thought, mood, perception, and consciousness.

Entactogens, or hallucinogenic amphetamines, are structural analogs of mescaline and amphetamine. The adverse effects of these drugs are many and are related to their sympathomimetic effects (12). Acute panic reactions have been demonstrated but are generally not dose-related; instead, they are a function of personal predisposition and circumstance (10). The patient in this case has a history of depression and suicidal ideation that was clearly intensified by the ingestion of DOI. There are a limited number of cases reporting the use of this drug. Shulgin notes that DOI is among the most potent and long-lived of the phenethylamine psychedelics (13).

According to news reports in 2007, three people in the United Kingdom were hospitalized after reportedly taking DOI at a rave (6, 7). A case report in 2008 involved a young man who experienced tonic-clonic seizures and required intubation after reportedly ingesting DOI, but was later found to have ingested a combination of a similar compound, DOC (2,5-dimethoxy-4-chloroamphetamine), and MDMA (14).

In June 2008, the Drug Enforcement Administration's *Microgram Bulletin* reported on blotter paper presumed to contain LSD in Florida. When analyzed by gas chromatography, one sample was found to be DOI and the other DOC. This was the first submission to the Drug Enforcement Administration of DOI in any form. In the United States, submissions of "blotter acid" containing LSD are uncommon. Most blotter papers contain either a hallucinogenic tryptamine or phenethylamine (11).

Analysis

2C-I has a molecular formula of $C_{10}H_{14}INO_2$ and a molecular weight of 307. As a primary alkylamine, it would be expected to have a base peak of 30 amu. DOI has a formula of $C_{11}H_{16}INO_2$ and a molecular weight of 321, with a predicted base peak of 44 amu due to the position of a methyl group on the carbon adjacent to the primary amine. The relevant spectrum in this case had the latter base peak (Figure 2). No metabolites were detected in this urine sample, and comparison to a spectrum of 2C-I provided by the Drug Enforcement Administration clearly ruled out the presence of 2C-I. Derivatization of the urine sample with propylchloroformate produced the expected propylformate derivative with a molecular weight of 407 amu and a base peak of 130.

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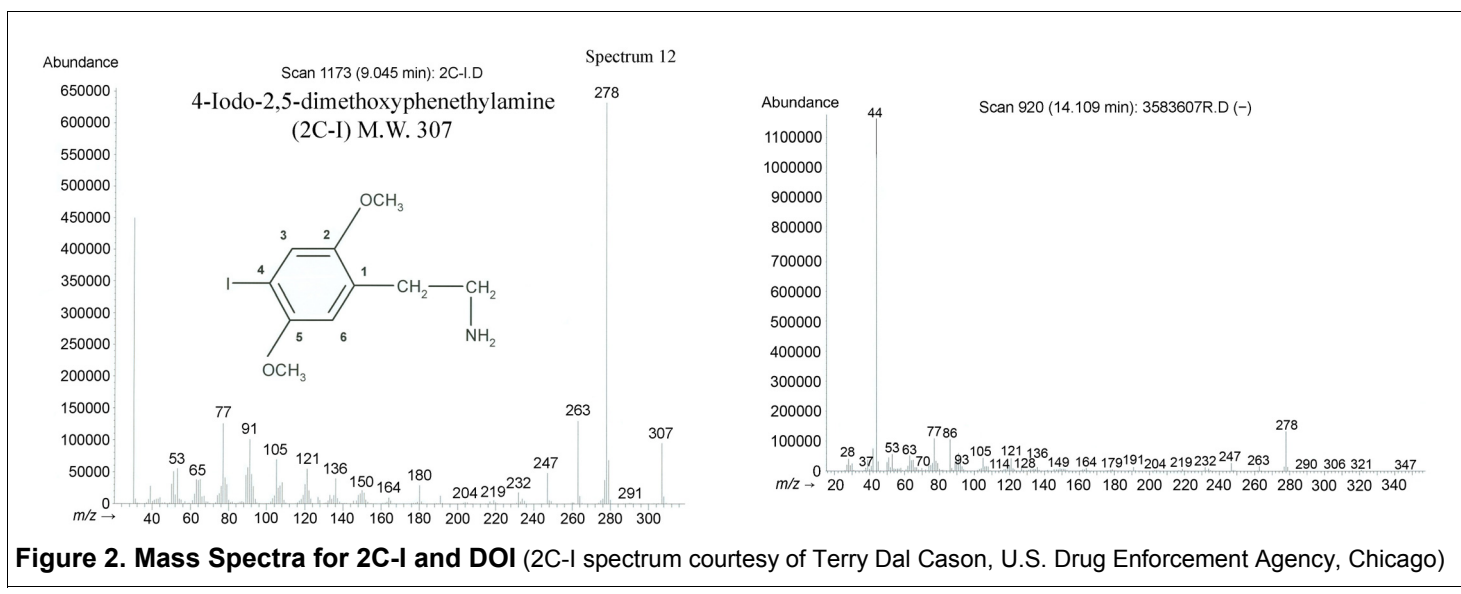


Figure 2. Mass Spectra for 2C-I and DOI (2C-I spectrum courtesy of Terry Dal Cason, U.S. Drug Enforcement Agency, Chicago)

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Federal Testing Revisions to Go into Effect Next May

By Susan Crumpton

Revisions to the mandatory guidelines for federal workplace drug testing programs will go into effect on May 1, 2010. The Substance Abuse and Mental Health Services Administration (SAMHSA) published the final notice of these revisions in the *Federal Register* on Nov. 25, 2008 (1), followed by a corrected effective date on Dec. 10, 2008 (2).

The guidelines affect drug tests performed for approximately 1.8 million federal employees and job applicants as well as tests for millions more public and private sector employees whose employers model their testing programs on the guidelines.

The changes will eventually affect the U.S. Department of Transportation (DOT) program, which plans to revise its workplace drug-testing regulations to harmonize with the revised SAMHSA guidelines (3). Roughly 12.1 million transportation employers, safety-sensitive transportation employees, and service agents are tested under the DOT regulations.

The entire guidelines document has been reorganized and rewritten to clarify requirements. Additional detail has been added to many areas to encourage consistent interpretation and compliance.

SAMHSA is in the process of developing and revising procedures and supporting documents, such as the federal custody and control form. Interested parties should monitor the SAMHSA website (www.workplace.samhsa.gov) and the *Federal Register* (www.archives.gov/federal-register) to stay up to date on revisions in policies and documents as well as issues related to them.

Requirements for urine specimen collection

Each specimen is to be collected as a split specimen. Single specimen collections will no longer be allowed. Consistent with current requirements for split specimen testing, Bottle A will be the primary specimen used for testing, while Bottle B will be stored unopened by the laboratory. Only the test subject, through the medical review officer (MRO), may request that Bottle B be tested at another certified laboratory after the primary specimen has been reported as positive, adulterated, or substituted.

SAMHSA reworded and reorganized the urine specimen collection procedures to provide additional detail and clarification and to be consistent with collection procedures in the current DOT regulations. For example, the new guidelines describe when and how a direct-observed collection is performed, when and how a monitored collection is performed, when the collector is to report a refusal to test, and the actions required of a collector and MRO when a donor does not provide a sufficient volume of urine.

Standards for collectors

The new guidelines include specific requirements for an individual to be a collector for federally regulated specimens and for an individual to be a trainer of collectors. These standards focus on knowledge of the specimen collection procedures in the guidelines, knowledge of federal agency guidance, completed training by a qualified trainer (i.e., training topics are specified), demonstrated proficiency through mock collections, and refresher training every five years. In addition, collectors must maintain their training records and provide them to a federal agency on request. Federal agencies must ensure that collectors meet guideline requirements before allowing them to collect workplace specimens.

The guidelines also specify the requirements for an individual to be an observer at a direct-observed collection. An observer is not required to be a trained collector. However, the observer must be trained in the steps of a direct-observed collection and have received training in topics such as maintaining the integrity of the collection process, ensuring donor privacy, ensuring that the collection is performed in a professional manner, and ensuring the

security of the specimen. Without exception, the observer must be the same gender as the donor.

Standards for collection sites

SAMHSA has redefined "collection site" to clarify that collections may be performed in temporary as well as permanent facilities. The guidelines include requirements for the physical facility, for collection site records, and for procedures to ensure the security and integrity of specimens.

There are new requirements for federal agency oversight of their collection sites, including annual inspections of randomly selected collection sites (at least 5%, up to 50). In addition, federal agencies must investigate reported collection site deficiencies, such as specimens rejected due to collection errors.

Revised standards for MROs

The 2010 guidelines revise the requirements for individuals to serve as MROs for federally regulated drug-testing programs and clarify their responsibilities. The current requirement for an MRO to be a licensed physician remains, with the added specification that the individual must have either a doctor of medicine or doctor of osteopathy degree. New MRO requirements include knowledge regarding the pharmacology and toxicology of illicit drugs, satisfactory performance on an examination by an MRO oversight group (whose qualifications and certification examination have been approved by SAMHSA), and training on specific topics.

For quality assurance, each federal agency is required to send blind samples to the facilities that test their workplace specimens. In the revised guidelines, MROs are specifically tasked to perform the initial investigation into inconsistent blind sample results, in contrast to current practice, in which SAMHSA investigates problems reported with such testing. Under the revised guidelines, if the MRO's investigation does not resolve the problem, the MRO is to notify both the federal agency and SAMHSA. SAMHSA will then investigate the issue and provide feedback to the federal agency and, as warranted, to all federal agencies whose specimens are tested by that test facility.

Instrumented initial test facility

A major change for federal workplace programs is the introduction of a new type of testing facility that can perform initial drug tests and first tests to determine specimen validity, the instrumented initial test facility (IITF). Historically, SAMHSA has required that testing be performed only in full-service laboratories that provide initial and confirmatory testing in the same facility. An IITF must be certified

Alternate Fluids Not Allowed

Although the new guidelines for federal workplace drug testing institute many changes, one current practice will remain unchanged. Despite continued interest in the use of alternative fluids such as hair, sweat, and oral fluid, in the SAMHSA guidelines to go into effect on May 1, 2010, urine will continue to be the only fluid approved for testing. "Significant issues have been raised by federal agencies during the review process for these alternate tests," the guidelines state (1). A further review by the agency is expected.

Reference

1. Substance Abuse and Mental Health Services Administration, U.S. Department of Health and Human Services. Mandatory guidelines for federal workplace drug testing programs. Fed Regist 2008 Nov 25;73(228):71857-907.

under SAMHSA's National Laboratory Certification Program (NLCP). The NLCP will have IITF application, inspection, and proficiency testing processes analogous to current NLCP processes for full-service laboratories.

IITFs will be allowed to report specimens as negative, negative and dilute (with creatinine between 5 and 20 mg/dL), or rejected. The IITF must forward specimens to a certified laboratory for testing when IITF test results indicate the specimen *may* be positive, adulterated, substituted, invalid, or dilute with creatinine less than or equal to 5 mg/dL. The certified laboratory will test and report specimens received from an IITF as if they had not been tested before. This will ensure that each specimen report is based on a complete forensic record of testing performed at a single certified facility, with data reviewed and certified by a qualified individual.

SAMHSA has specified the key personnel required for an IITF, along with requirements for their experience and education. The procedures described for IITFs include security, specimen accessioning, chain-of-custody documentation, testing, quality control and quality assurance, reporting, and method validation. In these areas, the IITF will be subject to the same requirements as a certified laboratory. The IITF's compliance with the guidelines' requirements will be verified through NLCP processes, including on-site inspections and a quarterly proficiency testing program. The NLCP procedures for IITF oversight will include specimen tracking through final reporting via NLCP records audits at IITFs and the certified laboratories to which IITFs forward specimens.

Revised testing requirements

The revised guidelines introduce new drug-test analytes into federal testing. The new initial drug-test analytes are 6-acetylmorphine (6-AM, the unique metabolite for heroin), and methylenedioxy-methamphetamine (MDMA, commonly known as ecstasy).

The current guidelines require confirmatory 6-AM testing of all morphine-positive specimens. The revised guidelines will require all specimens tested for opiates to also be tested for 6-AM using an initial immunoassay test, with confirmatory testing of presumptive positives, and no link between 6-AM testing and morphine results.

Initial testing for amphetamines must include testing for MDMA, which is not routinely tested for in workplace programs under the current guidelines. Specimens positive for MDMA by the initial test must be referred for confirmatory testing for MDMA, as well as two other new confirmatory test analytes: methylenedioxyamphetamine (MDA) and methylenedioxyethylamphetamine (MDEA).

SAMHSA is also lowering the test cutoffs for amphetamines and cocaine. For amphetamines, the initial test cutoff is being lowered to 500 ng/mL, with the confirmatory test cutoff lowered to 250 ng/mL for both methamphetamine and amphetamine. The amount of amphetamine required to be present to report a positive methamphetamine is being lowered to 100 ng/mL. For cocaine, the initial test cutoff is being lowered to 150 ng/mL, with the confirmatory cutoff for cocaine metabolite (benzoylecgonine) lowered to 100 ng/mL.

New confirmatory drug testing technologies

Gas chromatography/mass spectrometry (GC/MS) has been considered the gold standard in forensic drug testing and has been the only confirmatory test allowed since the guidelines were first implemented in 1988. The revised guidelines will allow new confirmatory methods.

These new methods must combine chromatographic separation and mass spectrometric identification (for example, tandem mass spectrometry and coupled methods using liquid chromatography), and must meet the guidelines' requirements for method validation, quality control, and quality assurance to ensure that results are accurate and forensically defensible.

Allowing laboratories to use these different methods will meet SAMHSA's mandate to ensure that the most appropriate technology available is used in regulated workplace testing programs.

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Cocaine Cutting Agent

Continued from page 1

2 illustrates the prevalence of three major pharmaceutical cutting agents in seized U.S. cocaine exhibits from January 2008 to April 2009. Levamisole's racemic analog, tetramisole, has not been identified in any seizures. The proportion of "uncut" cocaine seizures decreased from 64% to 22% in the same two-year period (2).

Why levamisole?

The "million-dollar" questions are: Why would a former chemotherapeutic agent and hog dewormer be used as a cutting agent? Why the dramatic increase in use?

The answers remain elusive. Levamisole may function as a central nervous system stimulant by acting as a ganglion nicotinic acetylcholine receptor agonist (6). In a rat model, the drug elevates dopamine and endogenous opiate (codeine, morphine) levels in various brain regions (7). Therefore, levamisole may fulfill one cutting agent criterion, namely, to provide a similar or complementary effect to the primary drug.

Side effects

The major side effect attributed to levamisole is agranulocytosis, manifested primarily as severe neutropenia (8), possibly through the generation of IgG and IgM anti-neutrophil antibodies, HLA Class 1 an-

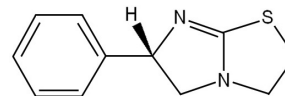


Figure 1. Chemical Structure of Levamisole

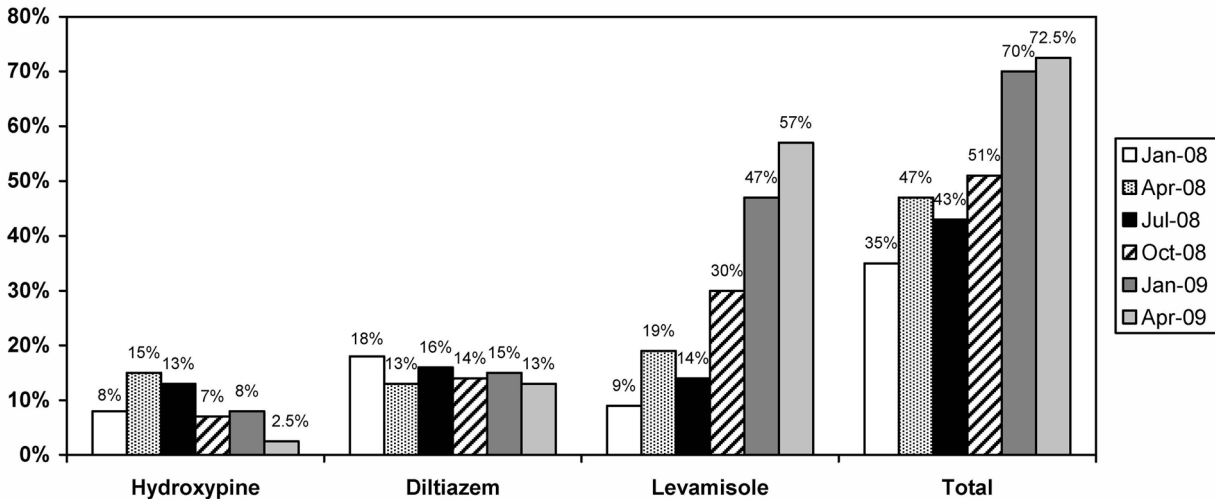


Figure 2. Prevalence of Three Major Cutting Agents in Cocaine Seized in the United States (2)



Public Health Division
Medical Office of Health

Neutropenia related to levamisole-adulterated cocaine
QUICK RESPONSE SHEET

What to look for:

- Any signs of infection, including fevers. Including any skin, abscess or lung infections that appear to have developed more rapidly or have progressed more seriously.
- Suspected cocaine use.

Diagnostic Tests:

- Urgent CBC and differential to look for neutropenia.
 - A spot urine specimen (minimum 10 mL) should be collected for cocaine metabolites and levamisole toxicology testing **as soon as possible** — the latter drug has a short detection window in urine (ideally specimen should be collected within 24–48 h of use).
- Specify **"neutropenia"** and **"levamisole toxicity suspected"** in the *Clinical information* section of the requisition. Contact your referral toxicology laboratory if more information is required.

Treatment:

If the neutrophil count is less than 1.0 and the patient is febrile or has an active infection, **an urgent referral to an on-call Hematologist** should be made.

The patient will require admission to hospital immediately, an infectious work-up including blood cultures should be undertaken and broad-spectrum intravenous antibiotics (ie. Piperacillin/Tazobactam, Imipenem or Ceftriaxime) administered. Filgrastim (G-CSF) should be started until consultation with a hematologist has been made. An additional investigation that can aid in the diagnosis is an elevated aPTT from a lupus anticoagulant which has been seen as well.

Recovery generally occurs after 7–10 days, but close monitoring is required as the risk of mortality from sepsis is high.

Interviews with Client:

Advise clients that the cocaine being sold is potentially cut with a dangerous substance that could harm their immune systems. If possible, inquiry about client's cocaine use practices, specifically related to the last time they used.

- **Type of cocaine use:** Crack Powder
- **Method of cocaine use:** Smoke Inject Snort
- **Amount of cocaine use:** Number of grams used: _____
Number of days used: _____
- **Did the cocaine have a unique taste, smell or look to it?**
- **Do they consistently use the same drug supplier?** Yes No
- **Amount purchased from last supplier:** Number of grams: _____

Contact Public Health Department:

If clinicians become aware of any more cases, contact public health with the patient's name, date of birth, PHN, address and phone number as we are monitoring the situation. Contact: Lewinda Knowles (780) 413-7740.

Figure 3. AHS Quick Response Sheet on Adulterated Cocaine

tigens, and anti-neutrophil cytoplasmic antibodies. Toxicological effects of cocaine adulterated with levamisole were not described until a 2008 Canadian case report of five patients with severe agranulocytosis hospitalized for fever and a variety of infectious complications in northern Alberta (9). The initial neutrophil count in each patient was 0×10^9 cells/L. One of the patients required admission to the intensive care unit. All other causes of neutropenia were ruled out, including medication use, nutritional deficiency, malignancy, and rheumatologic disorders. Urine toxicology testing confirmed the presence of cocaine or its metabolites and levamisole. All patients recovered following treatment with the granulocyte colony stimulating factor, filgrastim, and intravenous antibiotics.

In Alberta to date, there have been 12 toxicology-confirmed cases of agranulocytosis related to cocaine use, with 30 "probable" cases. Other jurisdictions in North America, including British Columbia, Colorado, and New Mexico, have reported cases. "Probable" cases are those patients with a history of cocaine use hospitalized for agranulocytosis and fever in which toxicology testing did not confirm the presence of levamisole.

As with testing for cocaine and its metabolites, GC/MS confirmatory

toxicology testing for levamisole in urine must be prompt, because the drug has a short elimination half-life of 5.6 hours. Furthermore, only 2–5% is excreted unchanged in urine.

Warnings

The Medical Office of Health in the Public Health Division of Alberta Health Services (AHS) has issued two notices to physicians and one general advisory to all Albertans on this health issue related to cocaine use. A *Quick Response Sheet* was circulated to physicians in January (Figure 3). Communications from AHS on this topic are at www.capitalhealth.ca/EspecialyFor/HealthProfessionals/default.htm.

The clinical toxicology laboratories at the University of Alberta Hospital and DynaLIFE_{Dx} append the following clinical alert to all confirmatory toxicology reports testing positive for both cocaine and levamisole: “Caution: Levamisole, a cocaine cutting agent, can cause acute, profound NEUTROPENIA. If this is the case, please contact Alberta Health Services.”

The use of levamisole as a cocaine cutting agent is a major public health concern. As stated by Zhu, et. al. (9), “Clinicians should consider the possibility of exposure to levamisole-adulterated cocaine in patients with otherwise unexplained fever and agranulocytosis.” In addition, toxicologists must do their part in identifying cocaine-levamisole scenarios to facilitate treatment.

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Readers are invited to submit questions they would like answered by an expert. An e-mailable PDF copy of this newsletter is available: cftnews@aacc.org.

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