A Cocaine Cutting Agent: The Potential for Profound Toxicity

DF LeGatt  Ph.D, FCACB
(don.legatt@albertahealthservices.ca)

Laboratory Medicine and Pathology
(U of A Hospital, Alberta Health Services/Faculty of Medicine and Dentistry, University of Alberta)

DynaLIFE_{Dx}

Edmonton, Alberta

BCSLS 2010
Sidney, British Columbia
Learning Objectives

Participants will be able to:
1. Describe various cutting agents used for cocaine.
2. Understand toxicity associated with the use of a relatively novel cutting agent.
3. Appreciate the importance of clinical laboratories in identification of these substances.
4. Appreciate the public health implications and become aware of initiatives undertaken to identify and combat this latest phenomenon.
Cutting agents are substances deliberately added to illicit drugs at some stage of production, packaging or distribution.

Rationale for adding such agents include:

1. Provide a similar or complimentary effect with a cheaper compound (e.g. procaine, lidocaine, benzocaine).
2. Attenuate side effects (e.g. diltiazem, hydroxyzine)
3. Extend the supply of illicit drug, thus increasing profits (e.g. salt, lactose, baking soda)
2005
Levamisole detected in urine extracts containing cocaine and its metabolites.
Chemical Structure of Cocaine

Chemical Structure of Levamisole
LEVAMISOLE

- Active l-isomer of tetramisole
- Discovered in 1966, Janssen Pharmaceutica, Belgium
- Original indication: antibiotic
- Eventual uses:
  - Anthelmintic in veterinary applications
    - BIG T Hog Dewormer Pellets 800 mg/Kg (Feed-Rite): 25 kg bags
    - Break-Away Hog Wormer Pellets
    - CO-OP Sow and Pig Wormer
  - Chemotherapeutic adjuvant to fluorouracil in colon cancer
  - Mechanism of action:
    - Immunomodulator
    - potentiates action of interferon and interleukin-2
    - restores hypofunctional T-lymphocytes and phagocytes to normal.
- Discontinued for human use in Canada, August, 2005
  - questionable toxicity, lack of clinical efficacy
- Health Canada Drug Product Database
  - 37 discontinued products
Levamisole Pharmacokinetics

Absorption: rapid, $t_{\text{max}} \sim 1$ to $2\text{h}$.

Metabolism: $\sim 97\%$ ($t^{\frac{1}{2}}: 5.6\text{h}$)
  - OMPI (phenylimidazolide)
  - active (levamisole a pro-drug?)
  - para-hydroxylation
  - glucuronidation
### LEVAMISOLE TOXICITY

- **Hematologic** – agranulocytosis (0.4 - 20%)
- **Hepatic** – increased ALT and bilirubin
- **Renal** – proteinuria
- **Respiratory** – dyspnea
- **Gastrointestinal** – diarrhea (~13%)
- **Dermatologic** – dermatitis (5 – 7%)
- **Neurologic** – fatigue, weakness (8%); seizures (rare)
- **Psychiatric** – irritability, anxiety, psychosis
Febrile Neutropenia

- Neutropenia: neutrophil < 1
- Agranulocytosis: neutrophil < 0.1
- Febrile Neutropenia:
  - Temp > 38°C + neutrophil < 1
  - Likely underlying severe infection
  - High mortality rate (2.5-20%)
Proposed Mechanism of Action

- Immune complex deposition on neutrophils → complement activation → cell lysis
- Anti-granulocytic antibodies
- Bone marrow suppression

Some shipments now contain dexamisole and tetramisole.

Percentage of Cocaine Bricks Containing Levamisole (U.S. Domestic Seizures)*

*Some shipments now contain dexamisole and tetramisole

Personal Communication, Dr. John Casale, U.S. Drug Enforcement Administration
Prevalence of three major pharmaceutical cutting agents in seized U.S. Cocaine Exhibits
(personal communication from Dr. J. Casale, Drug Enforcement Administration, U.S. Department of Justice)
Levamisole Adulterated Cocaine in Alberta

- Apr/06 - Mar/07: 0.4%
- Apr/07 - Mar/08: 2.7%
- Apr/08 - Nov/08: 11.0%
Cocaine/Levamisole Detection at UAH

% of cocaine confirmed specimens which also contain levamisole

- Aug-Oct/06: 6.9%
- Aug-Oct/07: 4.8%
- Aug-Oct/08: 44.8%
- Aug-Oct/09: 54.1%
Toxicology Testing for Levamisole

Cocaine Metabolite Immunoassay

(If positive or reading >20% above drug free specimen)

Gas chromatography/Mass Spectrometry

(GC/MS)
Toxicology Testing for Levamisole GC/MS

Urine Specimen (2 mL)

Extraction

Injection into GC/MS
Toxicology Testing for Levamisole GC/MS (cont.)

Data Acquisition

Data Interpretation/Verification
by comparison to authentic drug standards

1. Retention time (time to pass through system)
2. Fragmentation pattern (total ion mass spectra)
GC/MS Analysis: fragmentation pattern

Patient

Standard
Cocaine metabolite (ecgonine methylester)

amphetamine
methamphetamine

nicotine
methylecgonidine

acetaminophen
Caffeine

Cocaine metabolite (ecgonine methylester)

GC/MS Analysis

levamisole

codeine

gc

amphetamine
methamphetamine

cocaine

Caffeine

GC/MS Analysis
<table>
<thead>
<tr>
<th>Substance</th>
<th>Abundance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine artifact (methylcgonidine)</td>
<td>1.46e+07</td>
</tr>
<tr>
<td>ibuprofen</td>
<td>1.46e+07</td>
</tr>
<tr>
<td>levamisole</td>
<td>1.35e+07</td>
</tr>
<tr>
<td>Cocaine</td>
<td>1.30e+07</td>
</tr>
<tr>
<td>benzydamine</td>
<td>1.25e+07</td>
</tr>
<tr>
<td>metoclopramide</td>
<td>1.20e+07</td>
</tr>
<tr>
<td>levoamphetamine</td>
<td>1.15e+07</td>
</tr>
<tr>
<td>metoclopramide</td>
<td>1.10e+07</td>
</tr>
<tr>
<td>levamisole</td>
<td>1.05e+07</td>
</tr>
<tr>
<td>benzydamine</td>
<td>1.00e+07</td>
</tr>
</tbody>
</table>

**GC/MS Analysis**
## Drug Detection Time in Urine

<table>
<thead>
<tr>
<th>Drug Metabolite</th>
<th>Half Life</th>
<th>Drug Detection Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine Metabolites</td>
<td>4 - 6.5 hours</td>
<td>3 days</td>
</tr>
<tr>
<td>Levamisole</td>
<td>5.6 hours</td>
<td>2-3 days</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>6 hours</td>
<td>2-3 days</td>
</tr>
</tbody>
</table>

1) J Anal Toxicol. 2002;26:393-400.
Levamisole Impurities

- **Compound 202**
  - synthetic by-product of pharmaceutical process
  - found in impure batches of levamisole
  - 6-phenyl -2,3-dihydroimidazo [2,1b] thiazole

- **Compound 222**
  - formed during the “crack process”
    - cocaine HCL + NaHCO3 + heat
  - 3-(2-mercaptoethyl) -5-phenylimidazolidine-2-one

Both detected in urine specimens by GC/MS

??? Toxicity/“Clinical” Effect ???
levamisole

methadone

metabolite

Cocaine

methyladone metabolite

levamisole

levamisole impurity (compound 202)

GC/MS Analysis

GC/MS Analysis
GC/MS Analysis:
Fragmentation pattern

Patient

Standard

Library Searched: C:\DATABASE\UAHLIB.L
Quality: 64
ID: LEVAMISOLE IMPURITY 1 (6-phenyl-2,3-dihydroimidazo[2,1b]thiazole)(CPD 202)
Agranulocytosis After Consumption of Cocaine Adulterated With Levamisole

Background: Levamisole is a veterinary antihelminthic previously used as an immunomodulator in rheumatoid arthritis and as adjuvant therapy in the treatment of colorectal cancer. It is no longer available in North America for human use but is available in the United States and South America for veterinary administration.

Since 2004, pharmaceutical agents have been found in cocaine supplies in North America and Europe (1). Levamisole contaminated 30% of cocaine seized by the U.S. Drug Enforcement Agency from July to September 2008 (U.S. Department of Justice, Drug Enforcement Administration. Cocaine Signature Program Report. January–October 2008. Internal document.) and 11% of cocaine samples tested in Alberta, Canada, from April to December 2008 (Office of Research and Surveillance, Health Canada. Personal communication.). Levamisole causes reversible agranulocytosis in up to 20% of cases (2), but the clinical effects of cocaine adulterated with levamisole have not been described.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age and Sex</th>
<th>Levamisole &amp; Cocaine</th>
<th>Urine Other Positive Toxicology Findings</th>
<th>Blood Counts on Presentation</th>
<th>LAC</th>
<th>Clinical Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>38 F</td>
<td>+</td>
<td>Morphine, lidocaine, fluconazole, dimenhydrinate/diphenhydramine</td>
<td>Neutrophil (x 10^9 cells/L): 0</td>
<td>0.6</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+</td>
<td>Methamphetamine, amphetamine, pheniramine, morphine, dimenhydrinate/diphenhydramine</td>
<td>Total WBC (x 10^9 cells/L): 0</td>
<td>1.2</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>41 F</td>
<td>+</td>
<td>Lidocaine, zopiclone, 8 chlorotheophylline, dimenhydrinate/diphenhydramine</td>
<td>Neutrophil (x 10^9 cells/L): 0</td>
<td>2.2</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>18 F</td>
<td>+</td>
<td>Metoclopramide, benzydamine, ibuprofen</td>
<td>Total WBC (x 10^9 cells/L): 0</td>
<td>0.6</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>44 F</td>
<td>+</td>
<td>Acetaminophen, ketorolac, chlorpheniramine metabolite, thymol, polyethylene glycol, dimenhydrinate/diphenhydramine</td>
<td>Neutrophil (x 10^9 cells/L): 0</td>
<td>0.7</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>48 M</td>
<td>+</td>
<td>Clindamycin</td>
<td>Neutrophil (x 10^9 cells/L): 0</td>
<td>0.5</td>
<td>7</td>
</tr>
</tbody>
</table>
Findings

- Isolated agranulocytosis → neutrophil 0
- Recent cocaine exposure
- Previously healthy
- Vitamin B12 normal, Folate normal
- Other causes of neutropenia ruled out:
  - rheumatologic diseases
  - malignancy
  - medications
  - nutritional deficiency
Lupus Anticoagulant

- Acquired Antiphospholipid antibody
- Can be transiently induced by viral infections
- Seen with chronic levamisole use
- ? ↑ risk of thrombosis

Limitations

• Direct causation:
  – Did the levamisole come from the cocaine?
  – Did the levamisole cause the agranulocytosis?
    • In vitro stem cell growth
  – Was there another agent not detected causing the agranulocytosis?
• Specific characteristics at risk?
  – HLA-B27, rheumatoid arthritis
Canadian Addiction Survey 2004: Cocaine Use in the Last Year

<table>
<thead>
<tr>
<th>Region</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>British Columbia</td>
<td>2.6%</td>
</tr>
<tr>
<td>Alberta</td>
<td>2.4%</td>
</tr>
<tr>
<td>Saskatchewan</td>
<td>1.7%</td>
</tr>
<tr>
<td>Manitoba</td>
<td>2.0%</td>
</tr>
<tr>
<td>Ontario</td>
<td>1.3%</td>
</tr>
<tr>
<td>Quebec</td>
<td>2.5%</td>
</tr>
<tr>
<td>New Brunswick</td>
<td>1.1%</td>
</tr>
<tr>
<td>Newfoundland and Labrador</td>
<td>0.9%</td>
</tr>
<tr>
<td>Yukon</td>
<td>1.9%</td>
</tr>
<tr>
<td>Northwest Territories</td>
<td>1.1%</td>
</tr>
</tbody>
</table>
Canadian Addiction Survey 2004: Cocaine Use in Lifetime

- British Columbia: 16.3%
- Alberta: 12.3%
- Saskatchewan: 8.0%
- Manitoba: 8.9%
- Ontario: 8.7%
- Quebec: 12.2%
- New Brunswick: 4.2%
- Nova Scotia: 7.1%
- Newfoundland and Labrador: 3.7%
- Prince Edward Island: 5.5%
- Yukon: 10.6%
Canadian Addition Survey 2004: Cocaine Use in Lifetime

![Graph showing the increase in cocaine use from 1989 to 2004. The percentage of people using cocaine in lifetime increased from 3.5% in 1989 to 3.8% in 1994, and to 10.6% in 2004.](image)
The Alberta Response

Nov. 21, 2008: Province-wide alert to physicians

Nov. 28, 2008: Public health advisory

*Neutropenia related to levamisole adulterated cocaine*

(Quick Response Sheet for physicians)

http://www.capitalhealth.ca/EspeciallyFor/HealthProfessionals/default.htm
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 24-48h 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 culture: should be undertaken and broad-spectrum intravenous antibiotics (ie. Piperacillin/Tazobactam, Imipene or Ceftazidime) administered. Filgastrim (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 lup 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.
Levamisole Comment
Appended to Patient results

“Caution: Levamisole, a cocaine cutting agent, can cause acute, profound NEUTROPENIA.”
Latest Alberta Update
June 2009

• Confirmed Cases: 13
• Probable Cases: 32
• Other jurisdictions:
  – British Columbia (19)\(^1\)
  – Colorado
  – New Mexico
  – Washington
• More prevalent in women

Why Levamisole??

- Answer(s) remain elusive
- Theories:
  - May function as CNS stimulant:
    - Inhibition of presynaptic catecholamine uptake
    - Ganglion nicotinic acetylcholine receptor agonist
    - Elevated dopamine and endogenous opiate levels (codeine, morphine) in various brain regions (rat)

Case report

Levamisole tainted cocaine causing severe neutropenia in Alberta and British Columbia

Lewinda Knowles*1, Jane A Buxton2,3, Nataliya Skuridina3, Ifeoma Achebe4, Donald LeGatt5, Shihie Fan1, Nancy Yan Zhu6 and James Talbot1,4,7

Address: Edmonton Zone Medical Office of Health, Alberta Health Services, Suite 101 West Tower, 14310-111 Avenue, Edmonton, AB (T5M3Z7), Canada, 1Epidemiology Services, British Columbia Centre for Disease Control 655 West 12th Ave, Vancouver British Columbia (V6Z 4X4), Canada, 2School of Population and Public Health, University of British Columbia, 5804 Fairview Avenue, Vancouver British Columbia, (V6T 1Z3), Canada, 3Department of Medicine (Community Medicine), University of Alberta, Suite 4000 RTP, 8306 - 114 Street, Edmonton, Alberta (T6G 2V2), Canada, 4Department of Laboratory Medicine & Pathology, 484-08 Mackenzie Health Sciences Centre, University of Alberta Hospitals, Edmonton, Alberta (T6G 2R7), Canada, 5Department of Medicine (Hematology & Clinical Oncology), University of Alberta, 283 Walter Mackenzie Centre, Edmonton, Alberta (T6G 2B7), Canada and 6Department of Public Health Sciences, University of Alberta, 3-50 University Terrace, 8303 - 112 Street, Edmonton, Alberta (T6G 2T4), Canada

Email: Lewinda Knowles* - Lewinda.Knowles@albertahealthservices.ca; Jane A Buxton - Jane.buxton@bccdc.ca; Nataliya Skuridina - skuridina@telus.net; Ifeoma Achebe - Ifeoma.Achebe@albertahealthservices.ca; Donald LeGatt - Don.LeGatt@albertahealthservices.ca; Shihie Fan - Shihie.Fan@albertahealthservices.ca; Nancy Yan Zhu - nancy.zhu@ualberta.ca; James Talbot - James.Talbot@albertahealthservices.ca

* Corresponding author

Published: 17 November 2009


Received: 9 June 2009

This article is available from: http://www.harmreductionjournal.com/content/6/1/30

© 2009 Knowles et al; licensee BioMed Central Ltd.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

CMAJ

CMAJ • JANUARY 12, 2010 • 182(1)

© 2010 Canadian Medical Association or its licensors

Cocaine adulterant linked to neutropenia

Matthew O. Wiens PharmD, Wai Kon Son MD, Colin Ross PhD, Michael Hayden MD PhD, Bruce Carleton PharmD

Previously published at www.cmaj.ca

Hematopathology / Levamisole, Cocaine, and Agranulocytosis

Clinicopathologic Features of Agranulocytosis in the Setting of Levamisole-Tainted Cocaine

David R. Czuclewski, MD,1 Monica Brackney, MS,2 Christina Ewers, MSN,2 Jonaki Manna, MD,3 M. Howman Fekrazad, MD,4 Aftron Martinez,7 Kurt B. Noite, MD,1 Brian Hjelle, MD,1 Ian Rabinowitz, MD,1 Brian R. Curtis,5 Janice G. McFarland, MD,2 Joan Baumbach, MD,2 and Kathryn Foucar, MD1

Am J Clin Pathol 2010;133:466-472

DOI: 10.1309/AJCPQH6BPStH1W1
References


• Personal communication from Dr. John F. Casale, U.S. Department of Justice, Drug Enforcement Administration, Special Testing and Research Laboratory, Dulles, VA.


• Morley SR, Forrest ARW, Galloway JH. Levamisole as a Contaminant of Illicit Cocaine. Int Assoc Forensic Toxicol 2006; 44: 6 [abstract].


• Davis KL, Charney D, Coyle JT, Nemeroff C (Eds.) Neuropsychopharmacology: The Fifth Generation of Progress 2002; Lippincott Williams & Wilkins.


Phenacetin
Another Cutting Agent?
Thank you for your attention.

Questions?