Do You Know What You’re Snorting?
(Cocaine Cutting Agents – A Discussion)

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

Roundtable Session R305
IATDMCT 2009, Montreal
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)
November, 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
  e.g. - 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: $\sim 97\%$ (t½: 5.6h)
- 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

   http://www.stratfor.com/analysis/canada_and_transcontinental_drug_links
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)
Percentage of Cocaine Bricks Containing Levamisole
(U.S. Domestic Seizures)*

* Personal Communication, Dr. John Casale, U.S. Drug Enforcement Administration
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

- Aug/06 - Oct/06: 6.9%
- Aug/07 - Oct/07: 4.8%
- Aug/08 - Oct/08: 44.8%
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)
levamisole
methamphetamine
methylenebromidine
acetaminophen
fentanyl
cyclobenzaprine
zopiclone

GC/MS Analysis

GC/MS Analysis
Cocaine artifact (methyleneleconidine)
ibuprofen
levamisole
benzydamine
metoclopramide
Drug Detection Time in Urine

<table>
<thead>
<tr>
<th>Drug</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
methadone
levamisole impurity (compound 202)

GC/MS Analysis

Cocaine

Abundance
9.5e+07
9e+07
8.5e+07
7.5e+07
7e+07
6.5e+07
6e+07
5.5e+07
5e+07
4.5e+07
4e+07
3.5e+07
3e+07
2.5e+07
2e+07
1.5e+07
1e+07
5e+000

Time→
2.00 3.00 4.00 5.00 6.00 7.00 8.00 9.00 10.00 11.00 12.00 13.00 14.00 15.00 16.00 17.00 18.00 19.00
GC/MS Analysis:
Fragmentation pattern

Patient

Standard
Agranulocytosis After Consumption of Cocaine Adulterated With Levamisole -- Zhu et al...

Annals of Internal Medicine
Established in 1922 by the American College of Physicians

Home | Current Issue | Past Issues | In the Clinic | ACP Journal Club | CME | Collections | Patient Information
Audio/Video | Mobile | Subscribe | Tools | Help | ACP Online

Institution: University of Alberta | Sign In via User Name/Password

LETTER

Agranulocytosis After Consumption of Cocaine Adulterated With Levamisole

Nancy Y. Zhu, MD; Donald F. LeGatt, PhD; and A. Robert Turner, MD

17 February 2009 | Volume 150 Issue 4

Background: Levamisole is a veterinary antihelminthiac 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>Other Positive Toxicology Findings</th>
<th>Neutrophil (x 10⁹ cells/L)</th>
<th>Total WBC (x 10⁹ cells/L)</th>
<th># Days until Neutrophil &gt; 1 x 10⁹ cells/L</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>0</td>
<td>0.6</td>
<td>9</td>
<td>+</td>
<td>Cellulitis, pneumonia, bacteremia (E.coli)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+</td>
<td>Methamphetamine, amphetamine, pheniramine, morphine, dimenhydrinate/diphenhydramine</td>
<td>0</td>
<td>1.2</td>
<td>8</td>
<td>+</td>
<td>Cystitis (Klebsiella pneumoniae), typhilitis</td>
</tr>
<tr>
<td>2</td>
<td>41 F</td>
<td>+</td>
<td>Lidocaine, zopiclone, 8 chlorotheophylline, dimenhydrinate/diphenhydramine</td>
<td>0</td>
<td>2.2</td>
<td>5</td>
<td>+</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>18 F</td>
<td>+</td>
<td>Metoclopramide, benzydamine, ibuprofen</td>
<td>0</td>
<td>0.6</td>
<td>6</td>
<td>+</td>
<td>Thrush, peritonsillar abscess, cellulitis</td>
</tr>
<tr>
<td>4</td>
<td>44 F</td>
<td>+</td>
<td>Acetaminophen, ketorolac, chlorpheniramine metabolite, thymol, polyethylene glycol, dimenhydrinate/diphenhydramine</td>
<td>0</td>
<td>0.7</td>
<td>20</td>
<td>+</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>48 M</td>
<td>+</td>
<td>Clindamycin</td>
<td>0</td>
<td>0.5</td>
<td>7</td>
<td>+</td>
<td>Parotitis, face &amp; neck cellulitis, intubation with ICU admission for airway protection</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
• Appears to be chronic
• ? ↑ 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

2.6% YUKON
2.4% ALBERTA
1.7% BRITISH COLUMBIA
1.3% SASKATCHEWAN
2.0% MANITOBA
1.3% QUEBEC
2.5% NUNAVUT
1.1% NEW BRUNSWICK
1.1% NOVA SCOTIA
1.9% NEWFOUNDLAND AND LABRADOR
Canadian Addiction Survey 2004: Cocaine Use in Lifetime

16.3% 12.3% 8.0% 8.9% 8.7% 12.2% 7.1% 4.2% 5.5% 7.1% 3.7% 10.6%
Canadian Addition Survey 2004: Cocaine Use in Lifetime

Graph showing the increase in cocaine use from 1989 to 2004:
- 1989: 3.5%
- 1994: 3.8%
- 2004: 10.6%
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
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 toxicity 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 Ceftazidine) 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, inquire 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.
“Caution: Levamisole, a cocaine cutting agent, can cause acute, profound NEUTROPENIA. If this is the case, please contact Alberta Health Services, Public Health Division, 780-413-5034.”
Latest Alberta Update
June 2009

• Confirmed Cases: 13
• Probable Cases: 32
• Other jurisdictions:
  – British Columbia
  – Colorado
  – New Mexico
  – Washington
Why Levamisole??

• Answer(s) remain elusive
• Theories:
  – May function as CNS stimulant:
    • Ganglion nicotinic acetylcholine receptor agonist\(^1\)
    • Elevated dopamine and endogenous opiate levels (codeine, morphine) in various brain regions (rat)\(^2\)

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.