COCAINE
Do You Know What You’re Smoking or Snorting?

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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.

INTRODUCTION

- 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 isomer of tetramisole
- Original indication: antibiotic
- Eventual uses:
  - Anthelmintic in veterinary applications
    - e.g. 900 T/kg Dewormer Pellets 500 mg/Kg (Feed-Rite) 25 kg bags
    - Goat-Amyx Hog Wormer Pellets
    - CO-OP Sow and Pig Wormer
  - Chemotherapeutic agent in oesophageal cancer
  - Mechanism of action:
    - Immunomodulator
    - Potentiates action of Interferon and Interleukin-2
    - Reverses 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<sub>max</sub> ~ 1 to 2h.
Metabolism: ~97% (~5.6h)
- CMPI (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

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

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

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

<table>
<thead>
<tr>
<th>Quarter</th>
<th>Jan 06</th>
<th>Apr 06</th>
<th>Jul 06</th>
<th>Oct 06</th>
<th>Jan 07</th>
<th>Apr 07</th>
<th>Jul 07</th>
<th>Oct 07</th>
<th>Jan 08</th>
<th>Apr 08</th>
<th>Jul 08</th>
<th>Oct 08</th>
<th>Jan 09</th>
<th>Apr 09</th>
<th>Jul 09</th>
<th>Oct 09</th>
<th>Jan 10</th>
<th>Apr 10</th>
<th>Jul 10</th>
<th>Oct 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of Bricks</td>
<td>5</td>
<td>14</td>
<td>30</td>
<td>47</td>
<td>51</td>
<td>69</td>
<td>71</td>
<td>67</td>
<td>60</td>
<td>81</td>
<td>79</td>
<td></td>
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</table>

*Some shipments now contain dexamisole and tetramisole*
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)

Cocaine Cut with Levamisole in Alberta

Cocaine/Levamisole Detection at UAH

% of cocaine confirmed specimens which also contain levamisole
Cocaine Pharmaceutical Cutting Agents
UAH
Aug 1 – Oct 31, 2010

% of cocaine confirmed specimens containing cutting agent

Levamisole 63%
Diltiazem 8%
Phenacetin 4%

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)

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GC/MS Analysis: fragmentation pattern

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GC/MS Analysis

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Drug Detection Time in Urine

<table>
<thead>
<tr>
<th></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>

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 ???
GC/MS Analysis: Fragmentation pattern

Patient

Standard
**Agranulocytosis After Consumption of Cocaine Adulterated With Levamisole**

Nancy Y. Zhu, MD, Donald F. Leach, Ph.D, and A. Robert Turner, MD

17 February 2006 | Volume 150 Issue 4

Background: Levamisole is a veterinary anthelminthic widely used as an immunosuppressant in veterinary practice and as an adjuvant in the treatment of inflammatory bowel disease. 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-containing 25% of cocaine seized by the U.S. Drug Enforcement Agency from July to September 2004 (U.S. Department of Justice, Drug Enforcement Administration, Cocaine Signature Program Report, January–October 2005). Internal document ) and 11% of cocaine samples tested in Alberta, Canada, from April to December 2005 (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</th>
<th>Sex</th>
<th>Comorbidities</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 Clinical Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>38 F</td>
<td>+</td>
<td>Morphine, lidocaine, fluconazole, dimenhydrinate/diphenhydramine</td>
<td>0.6</td>
<td>0</td>
<td>Cellulitis, pneumonia, bacteremia (E.coli)</td>
<td>Cystitis (Klebsiella pneumoniae), typhilitis</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>41 F</td>
<td>+</td>
<td>Lidocaine, zopiclone, chlorotheophylline, dimenhydrinate/diphenhydramine</td>
<td>2.2</td>
<td>5</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>18 F</td>
<td>+</td>
<td>Metoclopramide, benzydamine, amitriptyline</td>
<td>0.6</td>
<td>6</td>
<td>Throat, peritonsillar abscess, cellulitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>44 F</td>
<td>+</td>
<td>Amitriptyline, ketorolac, chlorpheniramine, metabisulfite, polyethylene glycol, dimenhydrinate/diphenhydramine</td>
<td>0.7</td>
<td>20</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>48 M</td>
<td>+</td>
<td>Clindamycin, amikacin, amoxicillin, ampicillin, metronidazole</td>
<td>0.5</td>
<td>7</td>
<td>Parotitis, facial &amp; neck cellulitis, intubation with ICU admission for airway protection</td>
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</tr>
</tbody>
</table>
### Findings

- Isolated agranulocytosis $\rightarrow$ 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
- $? \uparrow$ 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
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
"Caution: Levamisole, a cocaine cutting agent, can cause acute, profound NEUTROPENIA."

Why Levamisole??

- Answer(s) remain elusive
- Theories:
  - May function as CNS stimulant:
    - Inhibition of presynaptic catecholamine uptake\(^1\)
    - Ganglion nicotinic acetylcholine receptor agonist\(^2\)
    - Elevated dopamine and endogenous opiate levels (codeine, morphine) in various brain regions (rat)\(^3\)

Levamicoke

In the (hopefully) near future, DanceSafe will be offering multiple use test kits through their website. These tests are very different from their past kits, and demand has been far greater than anticipated. With every kit handmade, it has been hard to keep up with the demand from Seattle.

www.levamicoke.info

COKE

Anything BUT the real Thing!!

References

- Personal communication from Dr. John F. Casale, U.S. Department of Justice, Drug Enforcement Administration, Special Testing and Research Laboratory, Dulles, VA.
Thank you for your attention.

Questions?