Chemical Agents of Opportunity for Terrorism: TICs & TIMs

Module Eight: Neurotoxicology

Lewis Nelson, MD, FACMT
Course Overview

1. Introduction / Principles of Medical Toxicology
2. Why Toxic Industrial Chemicals as Terrorist Weapons?
3. Inhalation of Toxic Industrial Gases
4. Agricultural Chemicals of Concern
5. Cyanide and Fumigants
6. Psychological Consequences of Mass Chemical Exposure
7. Risk Communication
8. Neurotoxins
9. Water, Food & Medication as Vectors
10. Delayed-Onset Toxins
11. Post-Event Medical Monitoring
12. Tabletop Exercise
Please help us improve this course by filling out the module evaluation.

You will receive an email with instructions following the conclusion of this presentation.
Faculty Disclosure

• Faculty: Lewis Nelson, MD, FACMT
  – Relationships with commercial interests:
  – Speakers Bureau/Honoraria: none
  – Consulting Fees: none
  – Other: none
Participant Question:

• How many people are in attendance at your site (including yourself)?
Central Nervous System

- The CNS is immensely complex
  - Great target for terrorism
- The CNS is central to both our function and our thinking
Objectives

• Recognize toxic syndromes that affect the nervous system
  – Sedation
  – Convulsions
  – Hallucinations

• Describe the unique clinical effects of toxins that cause sedation syndromes

• List examples of chemical agents of opportunity for each toxic syndrome

• Describe initial treatment strategy
The Balance of the Brain

- The brain is a fine balance of excitatory and inhibitory influences
  - Slight alterations in either direction are significant

- Excitation
  - Glutamate
  - Catecholamines

- Inhibition
  - Gamma-aminobutyric acid (GABA)
The Balance of the Brain

- In addition, other neurotransmitters influence our mood, our ability to think, remember, etc.
Clinical Syndromes of the CNS

Too much inhibition = Sedation/coma
Clinical Syndromes of the CNS

Too much stimulation = Convulsions
Clinical Syndromes of the CNS

Altered Modulation of Thoughts and Sensory Input = Hallucinations
Clinical Syndrome: Sedation

Excitation

Inhibition
Ethanol Intoxication: A Prototype for Sedative

• Dose-Response
  The more you drink, the drunker you get
  – 1 beer: buzz
  – 3 beers: intoxicated
  – 6 beers: uncoordinated, slurred speech,
    • Disinhibited
  – 18 beers: coma, respiratory arrest
Case Study: Moscow Theatre Hostage Crisis (2002)
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Case Study: Moscow Theatre Hostage Crisis (2002)
Case Study: Moscow Theatre Hostage Crisis (2002)

• Russian Federal Security Service pumped unidentified “gas” into building
• Security forces raided building
• 128 of 800 (16%) hostages died
  – All but one from gas
• All 42 separatists died
  – 39-41 from gas
What happened?
Chemical Agents of Opportunity for Terrorism: TICs & TIMs

Mike Hanna: Russia won't reveal gas used in rescue

Sunday, October 27, 2002 Posted: 1:46 PM EST (1846 GMT)

MOSCOW, Russia (CNN) -- The vast majority of deaths in a hostage standoff at a Moscow theater appear to have been caused by a sedative gas used to subdue the hostage takers, Russia's chief medical examiner said Sunday.

Of the 117 hostages who died, 115 apparently died from the gas, and more than 600 people who survived.

Lethal Moscow Gas An Opiate?

MOSCOW, Oct. 29, 2002

(CBS) The lethal gas that killed 116 Moscow theater hostages may be an opiate related to morphine, U.S. officials said Monday.

Such substances not only kill pain and dull the senses but also can cause coma and death by shutting down breathing and circulation.

Doctors from a Western embassy examined some of the former hostages and concluded "the agent they were exposed to appears consistent with an

Russia names Moscow siege gas

Wednesday, October 30, 2002 Posted: 9:11 PM EST (0211 GMT)

MOSCOW, Russia (CNN) -- Four days after Russian forces used anesthetic gas to end a hostage standoff by Chechen rebels, Russia's top health official identified the main component of the gas blamed for the deaths of 117 hostages.

The gas was based on derivatives of fentanyl, Health Minister Yuri Shevchenko said Wednesday.

Fentanyl is a potent narcotic used for anesthesia.

Fentanyl is an opiate-based narcotic 100
Characteristics of Opioids

<table>
<thead>
<tr>
<th>Agent</th>
<th>Potency (vs. morphine)</th>
</tr>
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<tbody>
<tr>
<td>Morphine</td>
<td>1</td>
</tr>
<tr>
<td>Meperidine</td>
<td>0.5</td>
</tr>
<tr>
<td>Methadone</td>
<td>4</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>300</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>4500</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>75</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>220</td>
</tr>
<tr>
<td>Carfentanil</td>
<td>10,000</td>
</tr>
</tbody>
</table>

**Chemical Agents of Opportunity for Terrorism: TICs & TIMs**

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**MATERIAL SAFETY DATA SHEET**

1401 Duff Drive, Suite 600  
Fort Collins, CO 80524  
(970) 484-6267  
January 3, 2000

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### Section 1 Identification

**Product Name**  
Wildnil®

**Product Description**  
An extremely potent opiate anesthetic used for rapid immobilization of free-ranging and captive members of Cervidae. Formulated at 4.40mg/ml Carfentanil Citrate, WILDNIL produces rapid immobilization following intramuscular injection.

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### Section 2 Hazardous Ingredients/Identity Information

<table>
<thead>
<tr>
<th>Hazard Components</th>
<th>CAS #</th>
<th>% by Wt</th>
<th>ACGIH TLV</th>
<th>OSHA PEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carfentanil Citrate</td>
<td>61380-27-6</td>
<td>0.45</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Sodium Chloride</td>
<td>7647-14-5</td>
<td>0.80</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Sterile Water for Injection</td>
<td>7732-18-5</td>
<td>98.55</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

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### Section 3 Physical/Chemical Characteristics

**Appearance:** Clear Liquid  
**Odor:** None  
**Boiling Point:** 100 °C  
**Specific Gravity:** 1.023  
**pH:** 3.0-4.5  
**Vapor Pressure:** 23.756 mmHg @ 25°C  
**Water Solubility:** Completely Soluble
Inhaled Sedatives

• Aerosolized drugs (dispersed liquids)
  – GABAergic agents
    • Benzodiazepine (e.g. diazepam)
    • Barbiturate (e.g. pentobarbital)
  – Opioids
  – Ketamine

• Volatile agents
  – Hydrocarbons
Sedatives

• Suspect whenever patients present with predominant CNS depression
  – Dose dependent

• Major complication: RESPIRATORY DEPRESSION
  – Respiratory depressant effect varies by agent

• Seek specific toxic syndrome:
  – CNS depression, pinpoint pupils, and respiratory depression = Opioid
  – CNS depression, normal examination and vital signs = Benzodiazepine
Management of Calmative / Sedative Poisoning

- Supportive care
  - Ventilation
- Antidotes for several are available
  - Of limited utility
Rapid Recognition leads to Urgent Intervention
Antidotal Treatment Strategy

Antidote: Naloxone (for opioids)
Participant Question:

What is the most important treatment for respiratory depression?

a) Artificial ventilation
b) Chest compressions
c) Naloxone
d) Oxygen
Clinical Syndrome: Convulsions
Convulsions

• The brain is a fine balance of excitatory and inhibitory influences
  – Slight alterations in either direction are significant
• “Inhibition of inhibition” is the most common cause of drug induced seizure
Inhibition of inhibition

Poisoning by an Illegally Imported Chinese Rodenticide Containing Tetramethylenedisulfotetramine — New York City, 2002

Illegally imported foreign products can result in domestic exposures to unusual toxic chemicals, and health-care providers might not be able to provide appropriate therapy because the chemical ingredients might not be listed or recognized even after translation of the product label. This report describes the first known case in the United States of exposure to a Chinese rodenticide containing the toxin tetramethylenedisulfotetramine (TETS), a convulsant poison. The report of this investigation highlights the need to prevent such poisonings through increased public education, awareness, and enforcement of laws banning the importation of illegal toxic chemicals.

On May 15, 2002, a previously healthy female infant aged 15 months living with her family in New York City was found by her parents to be playing with a white rodenticide powder that they had brought from China and applied in the corner of their kitchen. After 15 minutes, the child had generalized seizures and was taken to an emergency department. Her initial blood glucose level was 108 mg/dL (normal range: 80–120 mg/dL). Despite aggressive therapy with lorazepam, phenobarbital, and pyridoxine, she had intermittent generalized seizure activity for 4 hours and required intubation.
Man Admits Poisoning Food in Rival’s Shop, Killing 38 in China
By ERIK ECKHOLM
BEIJING, Sept. 17 — A jealous business rival has confessed to spiking the food in a snack shop in eastern China with rat poison, killing 38 people, mostly schoolchildren, and sending hundreds more to the hospital, state news organizations reported today.

Ending a two-day blackout on official reports about the poisoning, on Sept. 14, China Central Television and the New China News Agency said this evening that a man named Chen Zhengping had admitted to placing a potent rat poison in products of the Zhengwu Pastry Bar in Tangshan, a town near the city of Nanjing in Jiangsu Province.

Boarding school students and soldiers who relied on the shop for breakfast fell violently ill after eating fried dough sticks, sesame cakes and sticky rice balls on Saturday morning. Some patrons collapsed right in front of the shop, bleeding from the mouth and ears, witnesses said.

The accused man ran a rival shop and told the police that “he nursed a hatred because of business competition,” according to a television report.

By some accounts, Mr. Chen simply hoped to make patrons ill when he placed the toxin — a banned rodenticide called Dushuqiang, or “strong rat poison” — in the rival shop’s products.

But when people started dying, he fled and was arrested Sunday in Zhengzhou, 370 miles to the north, officials said. He has been returned to Nanjing, and investigation of the case continues, the police said.

Unconfirmed reports from a Hong Kong newspaper said Mr. Chen was a cousin of the owner of the shop whose food was poisoned, who by various accounts is in custody or in the hospital.

Dushuqiang contains tetramine, a chemical that attacks the nervous system, and was banned in 1991, officials said. But illegal production has continued in the countryside, and the poison has been used in other crimes, as well as in many suicides.

After early, sketchy accounts of the mass poisoning, China’s controlled news outlets said virtually nothing about the case over the last two days, spawning rampant speculation and conflicting accounts of the toll. Reports in some papers here and in Hong Kong have quoted unidentified Jiangsu officials as saying that 49 or more had died and hundreds more were seriously ill.

Tonight’s official report said 38 were dead and 6 others were in critical condition, while “most of the 200 victims” were in stable condition.

Personal grudges have been blamed for several bombings and poisoning incidents in China in recent years, but the toll this time was unusually high.
Tetramine

• Du-shu-quiang ("very strong poison")
• Used as a rodenticide in China
  – Banned in 1984
• Like many substances used as rodenticides, tetramine is highly toxic to humans
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RESEARCH ARTICLE

Tetramine poisoning in China: changes over a decade viewed through the media’s eye

Yi Li1, Yanxia Gao2, Xuezong Yu3, Jingmin Peng3, Fei Ma1 and Lewis Nelson4

Li et al. BMC Public Health 2014, 14:842
Some Chemical Causes of Convulsions

- Organophosphate & Carbamate Insecticides
- Nicotine
- Hydrazines
- Camphor
- Organochlorines
- Strychnine
Convulsions: Management

- Benzodiazepines
- Barbiturates, propofol
- Pyridoxine
  - Empiric dose, 5 gms (70 mg/kg)

Excitation
Inhibition

Antidote:
Benzodiazepine
Participant Question:

Convulsions from chemical toxins are typically due to which one of the following?

a) Hypoglycemia
b) Over-stimulation of the brain
c) Tetramine
d) Under-inhibition of the brain
“Playing with Our Mind”
Hallucinogens

- Alter modulation of thought processes
  - Serotonergic
  - Sympathomimetic
  - Anticholinergic
  - Anesthetic (PCP and ketamine)
Serotonergic Hallucinogens

- LSD
- Tryptamines (DMT, 5-MeO-DMT, psilocybin)
- Ololiuqui (morning glory seeds)
Serotonergic Hallucinogens

- 1968 - The Yippies (Youth International Party)
- Threatened to “space-out” or “turn on” the delegates to the Democratic National Convention in Chicago, and everyone else in Chicago as well, by dumping LSD into Lake Michigan.

Abbie Hoffman
Military Considerations

• Video
Anticholinergic Hallucinogens

Atropine, Scopolamine and Hyoscyamine
Clinical Effects

- Mad as a hatter
- Red as a beet
- Dry as a bone
- Hot as Hare
- Blind as a bat
- Full as a flask

(Also decreased GI motility)
"Modern" History

• 1676: a group of men led by Captain John Smith were sent to Jamestown, Virginia to quell the Bacon rebellion.

• Gathered the plant now known as “Jamestown weed” (or Jimsonweed), *Datura stramonium*, for a salad.
1676, Bacon Rebellion:

The soldiers presented a “very pleasant comedy, for they turned natural fools upon it for several days: one would blow a feather in the air; another would dart straws at it with much fury; and another, stark naked, was sitting up in a corner like a monkey, grinning and making mows at them….. A thousand such simple tricks they played, and after 11 days returned themselves again, not remembering anything that had passed.”

Robert Beverly, The History and Present State of Virginia (1705)
July 1995
Bosniaks fleeing Srebrenica during the war in Bosnia and Hercegovina.

“Survivors gave consistent descriptions of mortar shells that produced a ‘strange smoke’ of various colors which did not rise but spread out slowly. Following these attacks, some of the marchers - the numbers are unclear - began to hallucinate and behave in an irrational manner, with some even killing their friends or themselves. . . .”

BZ: 3-Quinuclidinyl benzilate (QNB)
Anticholinergic Hallucinogens

- Qualitatively similar

<table>
<thead>
<tr>
<th></th>
<th>Atropine</th>
<th>Scopolamine</th>
<th>BZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (70 kg)</td>
<td>8-14 mg</td>
<td>2 mg</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>Duration</td>
<td>4-8 h</td>
<td>2-4 h</td>
<td>48-72 h</td>
</tr>
</tbody>
</table>
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Treatment strategy

Antidote: Benzodiazepine
Participant Question:

Which best describes the clinical effects of hallucinogenic toxins used as terrorist weapons?

a) Incapacitating  
b) Lethal  
c) Sedating  
d) Unconcerning
Concluding Thoughts

- The CNS is a unique target organ for terrorism
- Limited number of acute clinical consequences
- Management is generally symptomatic although “antidotes” may be available for certain agents.
Questions?