Module Two
The Clinical Neurotoxicology of Chemical Terrorism

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Chemical Agents of Opportunity
Faculty Disclosure

- Faculty: Marco Sivilotti MD
  - Relationships with commercial interests:
    - Site investigator for phase III clinical trial (Shire)
    - Site investigator for phase III clinical trial (Affinimium)
  - Speakers Bureau/Honoraria: none
  - Consulting Fees: none
  - Other: none
Central Nervous System

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

• Recognize toxic syndromes that effect the nervous system
  – Sedation
  – Convulsions
  – Hallucinations
• Know unique clinical effects of toxins that cause sedation syndromes
• List examples of agents of opportunity for each syndrome
• Know 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

Inhibition

Glutamate

Catecholamines

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

- In addition, other neurotransmitters influence our mood, our ability to think, remember, etc.

Modulators of Thought Processes
- Serotonin
- Acetylcholine
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 = Hallucinations
Clinical Syndrome: Sedation

Excitation

Inhibition
Ethanol Intoxication: A Prototype for Calmatives

• Dose-Response
  – The more you drink, the drunker you get
  – 1 beer: buzz
  – 2 beers: intoxicated
  – 6 beers: uncoordinated, slurred speech,
    • Disinhibited
  – 24 beers: coma, respiratory arrest
Case Study: Moscow Theatre Hostage Crisis (2002)
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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?
Mike Hanna: Russia won't reveal gas used in rescue

Sunday, October 27, 2002 Posted: 1:48 PM EST (1946 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 were

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 an opiate-based narcotic used for anesthesia.
## Characteristics of Opioids

<table>
<thead>
<tr>
<th>Agent</th>
<th>Potency (vs. morphine)</th>
</tr>
</thead>
<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><strong>Fentanyl</strong></td>
<td><strong>300</strong></td>
</tr>
<tr>
<td>Sufentanil</td>
<td>4500</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>75</td>
</tr>
<tr>
<td>Remifentani</td>
<td>220</td>
</tr>
<tr>
<td><strong>Carfentanil</strong></td>
<td><strong>10,000</strong></td>
</tr>
</tbody>
</table>

MATERIAL SAFETY DATA SHEET

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

January 3, 2000

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 4.46mg/ml Carfentanil Citrate. WILDNIL produces rapid immobilization following intramuscular injection.

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>

Section 3 Physical/Chemical Characteristics

Appearance: Clear Liquid
Boiling Point: 100 °C
pH: 3.0-4.5

Odor: None
Specific Gravity: 1.023
Vapor Pressure: 23.756 mmHg @ 25°C
Water Solubility: Completely Soluble
“The use of pharmacological agents to produce calm behavioral state, particularly as relevant to management of individuals and/or groups that are agitated, aggressive and/or violent, is a topic with high relevance to achieving the mission of law enforcement and military communities”

(nldt2.arl.psu.edu/documents/calamative_report.pdf)
Inhaled Calmatives/Sedatives

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

• Volatile agents
  – Hydrocarbons
Calmatives/Sedatives

• Suspect whenever clinical picture presents with predominant CNS depression
  – All produce dose dependent sedation
• Major complication: RESPIRATORY DEPRESSION
  – Respiratory depressant effects vary
• Specific Toxic Syndrome: CNS depression, pinpoint pupils, and respiratory depression = Opioid
What is the most important treatment for patients who have respiratory depression?

1. Artificial ventilation
2. Chest compressions
3. Naloxone
4. Oxygen
5.
6.
7.
8.
9.
10.
Rapid Recognition leads to Urgent Intervention

Miosis
CNS Depression
Respiratory Depression

Narcan 0.4mL
Treatment strategy
Management of Calmative / Sedative Poisoning

• Supportive care
• Antidotes for several are available
  – Of limited utility
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

Illegal imports of 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 toxic tetramethylenedisulfotetramine (TETS), a convulsant poison. The report 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 tonight.

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 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 are 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
Rat Poison

61 students felled by rat poison in central China

BEIJING, Sept. 29 (Xinhuanet) -- Dozens of elementary school students and teachers in Hunan Province were hospitalized after ingesting rat poison with their school breakfasts in an apparent deliberate mass poisoning, state media said Sunday.

Sixty-one students from the Changhu Township Center Elementary School were in a hospital in the city of Yueyang, 23 of them in critical condition, said a city spokesman.

Investigators believe poison was deliberately placed in school food but don't have any suspects yet, said the spokesman.

All 317 students and staff who ate breakfast at the school on September 23 were sent to hospitals for checkups after their classmates and colleagues began vomiting and fainting, the Beijing Times newspaper said. People who ate the breakfast complained of head and stomach aches, it said.
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)
“Playing with Our Mind”
Hallucinogens

• Alter modulation of thought processes
  – Serotonergic
  – Sympathomimetic
  – Anticholinergic
  – Anesthetic (PCP and ketamine)
Sero
tonergic 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.
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.
Bacon Rebellion

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>
Treatment strategy

- Excitation
- Inhibition
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?