Module Two: Neurotoxins

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Course Overview
1. Introduction – Why Toxic Industrial Chemicals?
2. Inhalation of Toxic Industrial Gases
3. Neurotoxins
4. Agricultural Chemicals of Concern
5. Cyanide and Fumigants
6. Water, Food & Medication as Vectors
7. Delayed-Onset Toxins
8. Psychological Consequences of Mass Chemical Exposure
9. Tabletop Exercise

Please help us improve this course by filling out the course evaluation.

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

- Faculty: Lewis Nelson, MD
  - Relationships with commercial interests:
    - Site investigator for phase III clinical trial (Shire)
    - Site investigator for phase III clinical trial (Affinium)
  - 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**
- Glutamate
- Catecholamines

**Inhibition**
- Gamma-aminobutyric acid (GABA)

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
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)
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?
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>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>


Positive Purpose

“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)

October 3, 2000
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

Participant Question:
What is the most important treatment who have respiratory depression?

a) Artificial ventilation
b) Chest compressions
c) Naloxone
d) Oxygen
Rapid Recognition leads to Urgent Intervention

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
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
Chemical Agents of Opportunity for Terrorism: TICs & TIMs

Rat Poison

61 students fell by rat poison in central China

BEIJING, Sept. 28 (Xinhua) — Dozens of elementary school students and teachers in Hunan Province were hospitalized after ingesting rat poison with their school breakfast, in an apparent deliberate mass poisoning, state media said Sunday.

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

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

All 181 students and staff who ate breakfast at the school on September 23 were sent to the hospital 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 ache. 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)
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)

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 mooves 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)
Bosniaks fleeing Srebrenica during the war in Bosnia and Herzegovina.

"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."

Human Rights Watch

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?