Organophosphates Poisoning

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Objectives

By the end of this presentation, participants should be able to:

- Describe the symptoms of patients presenting with organophosphate poisoning
- Explain the mechanisms of toxicity for organophosphates
- Explain the mechanisms of action for atropine and pralidoxime
- Recommend a pharmacotherapeutic regimen for patients presenting with organophosphate poisoning
Epidemiology

- Three million organophosphate and carbamate agent exposures worldwide
  - 300,000 fatalities

- In 2008, there were 8000 reported exposures in the United States
  - < 15 deaths reported

- In 2012, there 4150 calls for organophosphate and carbamate exposures
  - 3 deaths
Organophosphate sources

- **Domestic (often not life-threatening)**
  - Surface sprays
  - Roach and other inset baits
  - Head lice shampoo

- **Industrial or occupational**
  - Crop protection
  - Fumigation

- **Terrorism or Warfare**
  - Sarin, tubin (E.g. Tokyo subway attack)
  - Very rapidly absorbed, deadly within minutes
Acetylcholine physiology

Normal metabolism of acetylcholine by acetylcholinesterase to choline and acetic acid.

From: The Clinical Basis of Medical Toxicology, Goldfrank's Toxicologic Emergencies, 10e, 2015
Mechanism of Cholinergic toxicity

Inhibited AChE (phosphorylated) cholinergic toxicity treatable with atropine and 2-PAM

Aging

Aged AChE

Cholinergic toxicity treatable with atropine not treatable with 2-PAM

No aging

Nonaged AChE

Cholinergic toxicity treatable with atropine treatable with 2-PAM
Organophosphate pharmacokinetics

- **Onset/Duration**: Depends on the agent’s rate of AChE inhibition, route, potency and total dose
  - **Oral/respiratory exposure**
    - Systemic effects
    - Within 3 hours
  - **Dermal exposure**
    - Often local effects (local diaphoresis, fasciculations)
    - Systemic effects (if any), up to 12 hours

- **Toxic dose**: ~5mL of concentrated form for agricultural use
Organophosphate pharmacokinetics

- **Metabolism**
  - Oxons
    - Directly inhibit acetylcholinesterase
  - Thions
    - Require desulfuration to the oxon form for maximal activity

- **Lipophilicity: can sequester in fats**
  - Lengthened toxicity
  - Can “repoison” with redistribution
<table>
<thead>
<tr>
<th>Anatomic Site of Action</th>
<th>Signs and Symptoms</th>
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<tbody>
<tr>
<td><strong>Muscarinic effects</strong></td>
<td></td>
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<tr>
<td>Sweat glands</td>
<td>Sweating</td>
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<tr>
<td>Pupils</td>
<td>Constricted pupils</td>
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<tr>
<td>Lacrimal glands</td>
<td>Lacrimation</td>
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<tr>
<td>Salivary glands</td>
<td>Excessive salivation</td>
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<tr>
<td>Bronchial tree</td>
<td>Wheezing</td>
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<tr>
<td>Gastrointestinal</td>
<td>Cramps, vomiting, diarrhea, tenesmus</td>
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<tr>
<td>Cardiovascular</td>
<td>Bradycardia, decrease in blood pressure</td>
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<tr>
<td>Ciliary body</td>
<td>Blurred vision</td>
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<tr>
<td>Bladder</td>
<td>Urinary incontinence</td>
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<tr>
<td><strong>Nicotinic effects</strong></td>
<td></td>
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<tr>
<td>Striated muscle</td>
<td>Fasciculations, cramps, weakness, twitching, paralysis,</td>
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<td></td>
<td>respiratory embarrassment, cyanosis, arrest</td>
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<tr>
<td>Sympathetic ganglia</td>
<td>Tachycardia, elevated blood pressure</td>
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<tr>
<td>Central nervous system</td>
<td>Anxiety, restlessness, ataxia, convulsions, insomnia,</td>
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<tr>
<td>effects</td>
<td>coma, absent reflexes, Cheyne-Stokes respiration,</td>
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<td></td>
<td>respiratory and circulatory depression</td>
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Organophosphate poisoning symptoms

- Cholinergic in nature (think DUMBBBELS or SLUDGE)
  - Bradycardia
  - Bronchospasm and expiratory wheezes
  - Diaphoresis
  - Miosis
  - Urination
  - Hyperperistalsis
    - Abdominal cramps and diarrhea
  - Excessive lacrimation
  - Excitation (anxiety)
  - Excessive salivation
  - Fasciculations and skeletal muscle weakness
    - Could lead to skeletal muscle paralysis (including respiratory muscles)
  - Convulsions
  - Coma
Life-threatening effects of organophosphate poisoning

Organophosphate insecticide effects after exposure

- Neuromuscular paralysis
- Bronchorrhea
- CNS depression
- Cardiovascular effects, e.g., bradycardia, hypotension

RESPIRATORY FAILURE

- Hypoxia

CIRCULATORY FAILURE

- Acidosis
- Myocardial dysfunction

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Organophosphate poisoning: Diagnosis

- **Toxidrome**
  - Based on physical exam and history

- **Clues**
  - Simultaneous presence of muscarinic and nicotinic toxicity
  - Triad
    - Miosis, bronchial secretions and muscle fasciculations

- **Laboratory measurement**
  - Detection of organophosphorus metabolites in urine
    - Para-nitrophenol or dialkyl phosphate
  - Erythrocyte cholinesterase activity
    - Best correlates with neuronal AChE
Toxicity management

- **Decontaminate**
  - Be careful when handling patient
    - Gloves, aprons
  - Skin contamination
    - Remove clothing
    - Wash skin with copious amounts of soap and water

- **If ingested within the hour**
  - Gastric lavage
  - Activated charcoal
Supportive treatment

- Circulation, Airway, Breathing
  - Depolarizing paralysis in severe poisoning
    - Intubation and Mechanical ventilation
      - If possible, avoid depolarizing neuromuscular blockers (e.g. Succinylcholine)
  - Increased secretions
    - Atropine/glycopyrrolate
    - Suctioning
  - Ventricular dysrhythmias, QT prolongation, Torsades

- Other manifestations
  - Hypotension
    - Pressors
  - Seizures
    - Benzodiazepines (10mg diazepam recommended)
Pharmacologic treatment

- **Antimuscarinics**
  - Atropine
  - Glycopyrrolate

- **Oxime therapy**
  - Pralidoxime

- **Benzodiazepines**
  - Diazepam
  - Lorazepam
  - Midazolam
Pharmacologic treatment: Atropine

- Indicated in all symptomatic patients
  - Can be diagnostic
- No effects on inhibited AChE or nicotinic receptors
- Competitively blocks the actions of acetylcholine on cholinergic and some central nervous system receptors
  - Alleviates bronchospasms and reduces bronchial secretions
- Can substitute glycopyrrolate to avoid anticholinergic toxicity

- Dosing
  - 0.05mg to 0.1mg/kg in children younger than 12
  - 2 to 5mg in adolescents and young adults
  - Repeat every 5 to 10 minute intervals until bronchial secretions and pulmonary rales resolve
    - Could take days
Pharmacologic treatment: Pralidoxime

- 2-pyridine aldoxime (Pralidoxime or 2-PAM)
  - Initiate as soon as possible
    - Prevents aging by reactivating enzymes
  - Breaks the covalent bond between the AChE and organophosphate; regenerates enzyme activity
  - Reverses nicotinic effects and muscular weakness/paralysis

- Dosing
  - 30 mg/kg then a maintenance infusion of 8 mg/kg/hour
Pharmacologic treatment: Kits

Mark-1 Autoinjector

DuoDote™
Monitoring

- Monitoring of vital signs

- Measurement of ventilatory capacity
  - Blood gases
  - Pulse oximetry
  - Leukocyte count with differentials
    - Pneumonia development

- Chest radiographs
  - Degree of pulmonary edema
  - Check for development of hydrocarbon pneumonitis
References
