I. Introduction

- Organophosphates (OPs) and Carbamates (CBs) are man-made cholinesterase inhibiting chemicals used primarily as insecticides but also as agents of chemical warfare. They are toxic through all routes of exposure. Even ocular exposure can lead to systemic effects with some agents.

II. Common names

- **OPs**
  - diazinon, chlorpyrifos (Dursban), dichlorvos, malathion, acephate (Orthene)

- **CBs**
  - carbaryl (Sevin), aldicarb (Temik), bendiocarb, methomyl (Lannate)

- **Nerve agents**
  - tabun, sarin, soman (These are also know as G agents as there were developed by the Germans during World War II), VX

III. Chemistry

- **OPs**
  - These agents are usually esters, amides or thiol derivatives of phosphoric acid

- **CBs**
  - These agents are N-substituted esters of carbamic acid.

IV. Mechanism of Toxicity

- **OPs** and **CBs** inhibit the function of a host of enzymes in the body (e.g. plasma and hepatic carboxylesterases, carboxylic ester hydrolases) but their main effect is the inhibition of the enzyme acetylcholinesterase (AChE), the enzyme which breaks down acetylcholine (ACh). For this lecture the two main cholinesterase enzymes of concern are erythrocyte and plasma (or pseudo) acetylcholinesterase.

- When AChE is inhibited, ACh builds up resulting in an overstimulation of muscarinic and nicotinic receptors and paralysis of cholinergic synaptic transmission in the CNS.
What happens at the cellular level?

In the case of OPs, the OP binds to an acyl pocket (where ACh typically binds to AchE) and then a phosphate group of the OP binds to the serine amino acid at the active site on the AChE molecule thus preventing it from functioning. This binding is irreversible for all practical purposes with spontaneous regeneration taking days to weeks. In some cases, ‘aging’ of the AChE molecule may occur when part of the OP is cleaved off and the rest is left attached to the AChE molecule making the enzyme permanently inactive.

- In the case of CBs, the carbamyl group will bind to the active site on the AChE molecule preventing its function. The main difference between the two agents with respect to their pathophysiologic effects is that unlike OPs, the effect of CBs on AChE is temporary with the carbamyl group spontaneously dissociating within 24 hours. This allows the activity of the AChE molecule to return to normal. Because of this, toxicity in CB poisoning is usually less severe.

IV. Adverse Effects

A. Acute

- OPs and CBs produce a distinct toxidrome (see the Table 1 below) depending on what area of the cholinergic nervous system is being effected. These areas are: muscarinic (postganglionic parasympathetic), nicotinic (sympathetic and parasympathetic ganglionic and somatic neuromuscular junction), and the CNS. A commonly used acronym to describe the muscarinic effects is SLUDGE which stands for Salivation, Lacrimation, Urination, Defecation, GI cramping and Emesis. However, although there is a distinct toxidrome, not every patient will present with the classic symptoms (e.g the muscarinic and nicotinic). It is possible to see nicotinic symptoms but only minimal, if any muscarinic symptoms and vice versa (especially in the elderly).
Table 1: Effects of systemic intoxication

<table>
<thead>
<tr>
<th>Muscarinic Effects</th>
<th>Nicotinic Effects</th>
<th>Central Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradycardia</td>
<td>Tachycardia</td>
<td>CNS Depression</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>Hypertension</td>
<td>Agitation</td>
</tr>
<tr>
<td>Bronchorrhea</td>
<td>Fasciculations</td>
<td>Confusion</td>
</tr>
<tr>
<td>Salivation</td>
<td>Mydriasis</td>
<td>Delirium</td>
</tr>
<tr>
<td>Lacrimation</td>
<td>Muscle Cramps</td>
<td>Coma</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>Weakness</td>
<td>Seizures</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Respiratory Paralysis</td>
<td>Slurred Speech</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td>Ataxia</td>
</tr>
<tr>
<td>Urinary Incontinence</td>
<td></td>
<td>Headache</td>
</tr>
<tr>
<td>Blurred vision</td>
<td></td>
<td>Fasciculations</td>
</tr>
<tr>
<td>Miosis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Time to Onset of the Acute Effects**
  The time of onset to these effects can vary. Route of exposure is one of these variables. Inhalation of some OPs/CBs can lead to development of symptoms within seconds as can transdermal exposure to some of the chemical warfare agents. Symptoms secondary to ingestion may take longer. Compounds such as those that require bioactivation (e.g. parathion) or those that are fat soluble with high volumes of distribution may take even longer to produce symptoms of toxicity. In general however, most patients will present with symptoms within minutes to a few hours of exposure.

B. Delayed
There are 3 different delayed neurological sequelae that may result from poisoning by these agents.

1. Intermediate Syndrome
   - Occurring 24-96 hours post exposure, this syndrome is characterized by progressive muscle weakness especially in the neck flexor and proximal muscles along with decreased or absent reflexes (esp. ankle and knee). It does not occur in every patient with significant poisoning. Recovery typically occurs in 2-3 weeks. The etiology of the syndrome is not well described but theories include inadequate use of antidotes and late partitioning of agents from fat stores to the motor end plates.

2. Organophosphate Induced Delayed Neurotoxicity or Polyneuropathy (OPIDN or OPIDP)
   - The onset of OPIDN is typically 1-3 weeks after the initial exposure. Symptoms include glove and stocking parasthesias (tingling/burning sensations in hands and feet), muscle weakness, ataxia, and loss of distal
tendon reflexes. Symptoms may progress to a bilateral flaccid symmetrical paralysis and eventually spasticity resulting in spinal cord injury. A marker enzyme, neuropathy target esterase (NTE), has been discovered that has assisted science in understanding the pathophysiology of this condition. It has been shown that OPs bind to NTE causing structural changes in the enzyme thus disrupting its function in axonal transport in neurons. It has also been shown through animal models that when 70% of NTE is inhibited, the symptoms of OPIDN develop. Whether or not NTE is inhibited by a specific OP is dependent on the structure of the OP (in other words, not every OP will cause NTE inhibition).

3. Other general CNS effects (may or may not be delayed in some cases)
   • Memory impairment, depression, personality changes, confusion, and peripheral neuropathies

V. Laboratory Monitoring
   • Both plasma (pseudo) and red blood (erythrocyte) cell cholinesterase levels should be obtained in every case of suspected significant poisoning.
   • Red blood cell cholinesterase levels are more difficult to obtain but are preferred as they more accurately describe the extent of intoxication.
   • There are significant differences between the 2 types of enzymes measured (See Table 2 below)
   • There are also some limitations of cholinesterase levels
     1. Neither is easily obtainable - few labs runs these levels making them more useful in confirming exposure vs actually assisting in treating the patient
     2. The normal range is based on population estimates – It is doubtful that a patient will have a known baseline AChE level prior to exposure that can be used to determine the extent of enzyme depression. (An exception may be if the patient being monitored for job surveillance such as a those people employed as pesticide applicators)
Table 2: Comparison of Red Blood Cell vs Plasma AChE

<table>
<thead>
<tr>
<th>Red Blood Cell (Erythrocyte) Acetylcholinesterase</th>
<th>Plasma (Pseudo) Acetylcholinesterase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocyte acetylcholinesterase is found in nerve tissue, brain and erythrocytes</td>
<td>Plasma acetylcholinesterase is a liver protein and circulates in the plasma</td>
</tr>
<tr>
<td>Erythrocyte acetylcholinesterase is a more accurate representation of nervous system acetylcholinesterase.</td>
<td>Plasma acetylcholinesterase levels are a less accurate representation of nervous system acetylcholinesterase</td>
</tr>
<tr>
<td>Erythrocyte acetylcholinesterase is more difficult to obtain</td>
<td>Plasma acetylcholinesterase is easier to assay, but declines faster</td>
</tr>
<tr>
<td>Regeneration without treatment occurs at about 1%/day</td>
<td>Regeneration without treatment occurs at about 25-30% in the first 7-10 days</td>
</tr>
<tr>
<td>Normalization of erythrocyte acetylcholinesterase levels occurs in 5-7 weeks</td>
<td>Normalization of plasma acetylcholinesterase levels occurs in 28-42 days.</td>
</tr>
<tr>
<td>Treatment with Pralidoxime normalizes erythrocyte acetylcholinesterase levels</td>
<td>Pralidoxime treatment may only slightly increase plasma acetylcholinesterase levels.</td>
</tr>
<tr>
<td>False depression of erythrocyte acetylcholinesterase levels may occur with pernicious anemia, hemoglobinopathies, antimalarial treatment, and oxalate blood tubes.</td>
<td>False elevation of plasma acetylcholinesterase levels may occur with liver dysfunction (cirrhosis), malnutrition, hypersensitivity reactions, drugs (succinylcholine, codeine, morphine), pregnancy, and genetic deficiency.</td>
</tr>
<tr>
<td>Erythrocyte Acetylcholinesterase level of 20-50% of baseline correlates with mild toxicity, 10-20% of baseline is consistent with a moderate exposure, and less than 10% of baseline is consistent with severe toxicity.</td>
<td></td>
</tr>
</tbody>
</table>


VI. Decontamination
   A. Dermal
      • Remove any clothing that may have come into contact with the organophosphate or body fluids.
      • Make sure nurses and physicians wear appropriate gloves (neoprene or nitrile should be used as latex is an ineffective barrier to OPs), masks, and personal protective equipment so they themselves do not become exposed.
      • Wash exposed area well at least twice with mild soap and water, to prevent and further contamination.
      • Be sure to wash hair and under nails.

   B. Ocular
      • Remove contacts if patient is wearing them.
      • Flush eyes with room temperature water for 15 minutes. Allow eye to heal for next hour. If eye is still red, irritated or if any vision abnormalities ensue, patient should be referred to a physician.
      • Avoid eye drops unless prescribed by physician.

   C. Inhalation
      • Remove patient from exposure area. Provide fresh air.
      • If respiratory irritation or shortness of breath persist or symptoms become worse refer patient to physician.

   D. Ingestion:
      • Syrup of ipecac and inducing emesis is contraindicated due to possible respiratory depression and seizures.

      • Gastric lavage may be indicated if patient presents soon after ingestion or a large amount of the organophosphate is consumed.

      • Activated charcoal 1-2 grams/kg should be administered with sorbital.

VII. Treatment
   A. Organophosphates

      1. ABC’s

      2. Respiratory supportive care, supplemental oxygen 100%. Monitor respiratory status and oxygen saturation closely, intubation may be required secondary to weakening of respiratory muscles and excessive bronchial secretions.

      3. Monitor cardiac rhythm, closely.
4. Obtain erythrocyte and plasma acetylcholinesterase level (prior to administration of 2-PAM or atropine if possible.), baseline electrolytes, ABG’s.

5. Avoid agents such as physostigmine, antihistamines, phenothiazines, which may potentiate anticholinesterase activity and depolarizing agents such as succinylcholine (used during intubation) which require cholinesterases to be deactivated. Avoid CNS depressants which may increase the risk of respiratory arrest.

6. Atropine is a competitive acetylcholine antagonist and should be used to alleviate excessive bronchial secretions, salivation, abdominal cramps, vomiting and bradycardia.

   • Adult Dose = 1-2 mg slow IV push for diagnosis and then 2-4mg slow IV push every 5-15 minutes until drying of secretions has occurred. Atropine can also be given IM if IV access is unavailable.

   • Child’s dose = 0.015mg/kg slow IV push for diagnosis and then 0.05mg/kg slow IV push every 5-15 minutes until drying of secretions.

   • Adverse effects of atropine include tachycardia, confusion, flushing, dilated pupil

   • The end point for atropine is drying of secretions. Large doses (up to hundreds of milligrams) of atropine may be needed within the first 24 hours.

7. Pralidoxime (2-PAM)

   2-PAM reverses the phosphorylation of the cholinesterase molecules by removing the phosphate moiety from the AChE molecule. It will also act as a scavenger for unbound OP. 2-PAM should be given within the first 24 hours to be the most efficacious, but may still be of some benefit 36-48 hours post exposure. It is synergistic with atropine with muscarinic effects resolving in most cases within 20-40 minutes. Insufficient dosing may lead to development of intermediate syndrome discussed previously.

   • Adults: 1-2 grams IV (20-40mg/kg), in 200ml D5W or NS over 30 minutes. 2-PAM can also be given IM if no IV access is available. This should then be followed by an infusion of 500mg/hr for 48 hours or until symptoms resolve in severely poisoned patients (e.g. muscle weakness, fasciulations).

   • Children: 25-40mg/kg in 200ml D5W or NS over 15 minutes
• Monitoring while on 2-PAM should include close observation of heart rate and blood pressure

• Adverse effects include neuromuscular blockade (secondary to rapid infusion), dizziness, nausea, vomiting, blurred vision

8. Treatment of seizures
• Seizures will often subside with atropine or 2-PAM treatment.

• If seizures do not subside with the above treatment, diazepam 5-10mg IV may be given over 3-5 minutes in adults. Diazepam has been shown in animal studies to improve survivability.

• Children may be given 0.24-0.4mg/kg over 3-5 minutes.

• Monitor for respiratory depression.

B. Carbamates

• Treatment is similar to that listed above for OPs. There has been some animal study data that would seem to suggest that use of 2-PAM in treatment of carbaryl poisoning may worsen outcomes so until further studies are completed, it is best to avoid use in these scenarios.

VIII. The Nerve Agents (sarin, tabun, soman, VX)

• All of these agents are extremely toxic, much more so than the OP insecticides with the human fatal dose for tabun and soman calculated at 0.01 mg/kg. A drop of sarin is sufficient to be lethal in humans. VX is a newer compound and is approximately 100 times more toxic than soman and 300 times more toxic dermally. They are toxic through all routes of exposure. The main difference between these agents and typical OPs (other than their increased potency) is their ability to ‘age’ AChE at a much higher rate making the use of antidotes such as 2-PAM less effective especially after 1-3 hours post exposure.

IX. References

1. Micromedex
4. Ellenhorn's Medical Toxicology, Mathew J. Ellenhorn, 1997
6. Clinical and Experimental Toxicology of Organophosphates and Carbamates, Ballantyne and Mars, 1992