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Thank You…

• …to COL J. Dave Barry for his work on previous versions of these slides
The Core Content of Medical Toxicology

2.2.7 Pesticides
   2.2.7.1 Fumigants and Sterilants
   2.2.7.2 Fungicides
   2.2.7.3 Herbicides
   2.2.7.4 Insecticides and Repellents
      2.2.7.4.1 Carbamates
      2.2.7.4.2 DEET
      2.2.7.4.3 Meth-balls
      2.2.7.4.4 Organochlorines
      2.2.7.4.5 Organophosphates
      2.2.7.4.6 Pyrethrins and pyrethroids
   2.2.7.5 Rodenticides
      2.2.7.5.1 Anticoagulant
      2.2.7.5.2 Nonanticoagulant
   2.2.7.6 Other (eg, molluscides)
Pesticides

- Insecticides
- Herbicides
- Fungicides
- Fumigants
- Molluscicides
Insecticides

- Cholinesterase inhibitors
  - Organophosphates
  - Carbamates
- Organochlorines
- Pyrethrins/Pyrethroids
- Newer insecticides
Cholinesterase Inhibitors

- Carbamates
  - Ordeal (calabar) bean

*Organic phosphorus compounds*

- Organophosphates
  - Synthesized
Cholinesterase Inhibitors

Acetylcholine + Choline → Acetic Acid
The Autonomic Nervous System

Sympathetic

Parasympathetic

Neurons (N) and Muscles (M)
Sympathetic

Parasympathetic (cholinergic)

C

T

N

S

N

M

agitation

Sz

miosis

motility

vasoconstriction

agonist

motor

micturition
Organophosphates
Delayed Syndromes

- Intermediate Syndrome
  - Weakness 1-4 d after exposure
  - Peripheral NMJ dysfunction
  - Ineffective AChE reactivation

- OPIDN
  - Neuropathy target esterase (NTE)
    - Lysophospholipase (lysoPLA)
  - TOCP (tri-ortho cresyl phosphate)
    - Jamaican ginger paralysis (1930s)
    - Cooking oils (1950s)
Tri-Ortho Cresyl Phosphate (TOCP)

- Jamaica Ginger extract ("Jake") – sold as medicinal in early 1900s
  - TOCP added as an adulterant during Prohibition
- Characteristic neurotoxicity
  - "Jake" walk / "Jake" paralysis
- Noted as classic example of OPIDN
Organophosphates Diagnosis

- RBC cholinesterase
  - Better reflection of synaptic inhibition
  - Regenerates more slowly than neuronal AChE
  - Wide variations
  - ↓ in RBC disorders

- Butyrylcholinesterase (pseudocholinesterase)
  - Falls first
  - Recovers rapidly (few days)
  - Wide daily variation
  - ↓ in other disorders (liver dysfxn, malnutrition, drugs, pregnancy, genetic deficiency)
Cholinesterase Inhibitor Treatment

- Decontamination
  - Protect providers
    - Glove
    - Bag
  - Skin
    - Triple wash – soap/water
    - Shave scalp?
  - GI
    - Gastric lavage?
    - AC?
Cholinesterase Inhibitor Treatment

- Decontamination
- Antimuscarinic agents
  - Atropine
    - Infusion 0.02-0.08 mg/kg/hr
    - Bolus 2 mg q2-15 min, double dose
  - Glycopyrrolate
  - Scopolamine
Cholinesterase Inhibitor Treatment

- Decontamination
- Antimuscarinic agents
- Benzodiazepines
  - Diazepam
Cholinesterase Inhibitor Treatment

- Decontamination
- Antimuscarinic agents
- Benzodiazepines
  (Organophosphates)
- Oximes
  - Pralidoxime – bolus (600 mg q4h, infusion 1-2 g load then 500 mg/hr)
  - Obidoxime, HI-6
Organophosphates

- Aging & oximes

Organophosphates

- Aging & oximes

Organophosphates

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Organochlorines

• Large family of neuroexcitatory toxins
  • DDT and analogues
  • Cyclodienes
  • Hexachlorocyclohexane (Lindane)
  • Mirex and chlordecone
Organochlorines

- Large family of neuroexcitatory toxins
- DDT and analogues
  - Most banned from industrialized countries
  - Na$^+$ channel blockade
  - Neuroexcitation

Dichlorodiphenyltrichloroethane (DDT)
Organochlorines

• Large family of neuroexcitatory toxins
  • DDT and analogues
  • Cyclodienes
    • Most banned from industrialized countries
  • GABA antagonists
  • Neuroexcitation

Aldrin
Organochlorines

• Large family of neuroexcitatory toxins
  • DDT and analogues
  • Cyclodienes
  • Hexachlorocyclohexane (Lindane)
    • Scabicide
    • GABA antagonist
    • Seizures, neuroexcitation

Lindane (hexachlorocyclohexane)
Organochlorines

• Large family of neuroexcitatory toxins
  • DDT and analogues
  • Cyclodienes
  • Hexachlorocyclohexane (Lindane)
  • Mirex and chlordecone
    • Hopewell epidemic (1974)
    • “Kepone shakes”
Pyrethrins/Pyrethroids

- Pyrethrins
  - Naturally occurring
  - Na$^+$ channel openers
  - Rapidly decompose

- Pyrethroids
  - Synthetic derivatives
  - More persistent/potent
  - Piperonyl butoxide (p450 inhibitor)
# Pyrethrins/Pyrethroids

<table>
<thead>
<tr>
<th>Substance</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrethrins</td>
<td>Allergic</td>
</tr>
<tr>
<td>Pyrethroids</td>
<td></td>
</tr>
<tr>
<td>Type I</td>
<td>Low toxicity in humans</td>
</tr>
<tr>
<td></td>
<td>“T” syndrome (tremor)</td>
</tr>
<tr>
<td>Type II</td>
<td>More potent</td>
</tr>
<tr>
<td></td>
<td>“CS” syndrome (choreoathetosis, salivation)</td>
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<tr>
<td></td>
<td>GI (N/V/D), pulmonary, neuroexcitation</td>
</tr>
</tbody>
</table>
Pyrethrins/Pyrethroids

- Treatment
  - Supportive
  - Decontamination
    - Skin
    - GI – activated charcoal
Other Insecticides

- Boric acid
  - Ant/cockroach killer
  - Mechanism unclear
  - Symptoms
    - GI (blue/green emesis/diarrhea)
    - Kidney
    - CNS/Neuro
    - Derm (boiled lobster rash)
Other Insecticides

- Amitraz
  - $\alpha_2$-agonist
- Fipronil
  - GABA receptor antagonist
  - Insect:Human :: 1000:1
- Neonicotinoids
  - Imidacloprid, thiamethoxam

- Avermectins (e.g., ivermectin, abamectin)
  - Formed from fermentation by Streptomyces avermitilis
  - Cause GABA release

- Treatment
  - Supportive
Herbicides

- Bipyridyl herbicides
  - Paraquat, diquat
- Chlorphenoxy herbicides
  - 2,4-D, 2,4,5-T, Agent Orange
- Glyphosate
- Anilide derivatives
Bipyridyl Compounds

- Paraquat/Diquat
Bipyridyl Compounds

- Paraquat
  - Active transport into Type I & II alveolar epithelial cells
  - Surfactant depletion, destruction of alveoli

Bipyridyl Compounds

- Symptoms
  - Dependent upon amount ingested
  - May be delayed, especially with dilute products
- Caustic (skin, GI mucosa)
- Renal toxicity/failure
- ARDS (paraquat – pulmonary fibrosis)
- CNS (somnolence, coma, seizures)
Bipyridylyl Compounds

- Treatment
  - Skin decontamination
  - Lavage (N/V usually occur though)
  - AC, Fuller's earth, bentonite, garden clay
  - Hemodialysis, hemoperfusion, hemofiltration
  - ? No O$_2$ until PaO$_2$ < 50 mm Hg
Chlorophenoxy Compounds

- Chemical analogs of auxins (plant growth hormones)
- Cause uncontrolled and lethal plant growth

2,4,5-Trichlorophenoxyacetic acid (2,4,5-T)
Chlorphenoxy Compounds

• Symptoms
  
  • GI: N/V, abdominal pain, diarrhea
  
  • CV: hypotension, nonspecific ECG abnormalities
  
  • CNS: coma, hypertonia, hyperreflexia
  
• Treatment: supportive

Ukrainian opposition presidential candidate Viktor Yushchenko
Glyphosate

- Plant mechanism: amino acid analogue
- Human mechanism: unclear
  - Difficult to separate toxicity of glyphosate from surfactants and other additives

- Symptoms
  - GI/caustic
  - Pulmonary (? Aspiration)
  - CV, renal, CNS toxicity

- Treatment: supportive
Anilide Derivatives

- **Symptoms**
  - Methemoglobinemia

- **Treatment**
  - Methylene blue
Fungicides

- Metallic/organometallic
  - Ba, Cu, Cd, Sb, Hg
- Substituted aromatics
  - Chlorothalonil, pentachlorophenol, hexachlorobenzene
- Thiabendazoles
  - Benomyl, terrazole, thiabendazole
Dithiocarbamates

- Most commonly used family of fungicides
- Not cholinesterase inhibitors
- Metabolized to carbon disulfide
  - CNS toxicity/peripheral neuropathy
- Disulfiram-like reactions
  - Inhibition of acetaldehyde dehydrogenase
Fumigants

- Phosphine – see rodenticides
- Methyl bromide
- Sulfuryl fluoride
Methyl Bromide

- Heavier than air
- Chloropicrin additive
- Phased out (ozone-depleting agent)

- Symptoms
  - Skin: irritation, blistering
  - Pulmonary: dyspnea, NCPE
  - CNS: tremor, seizure, coma, visual disturbances

- Treatment
  - Supportive
Sulfuryl Fluoride (Vikane)

- Heavier than air
- Chloropicrin additive
- Mechanism: suspected fluoride poisoning

Symptoms
- Skin: irritation, blistering
- CNS: paresthesias, tremor, seizure, coma
- CV: shock, cardiac dysrhythmias

Treatment
- Supportive; monitor Ca^{2+}
Molluscicides

- Quaternary ammonium compounds
- Carbamates
- Metals
- Metaldehyde
  - Toxic mechanism unclear; ? Acetaldehyde
- Symptoms
  - GI: N/V/D, abdominal pain
  - CNS: seizures, coma, hyperthermia
Questions?