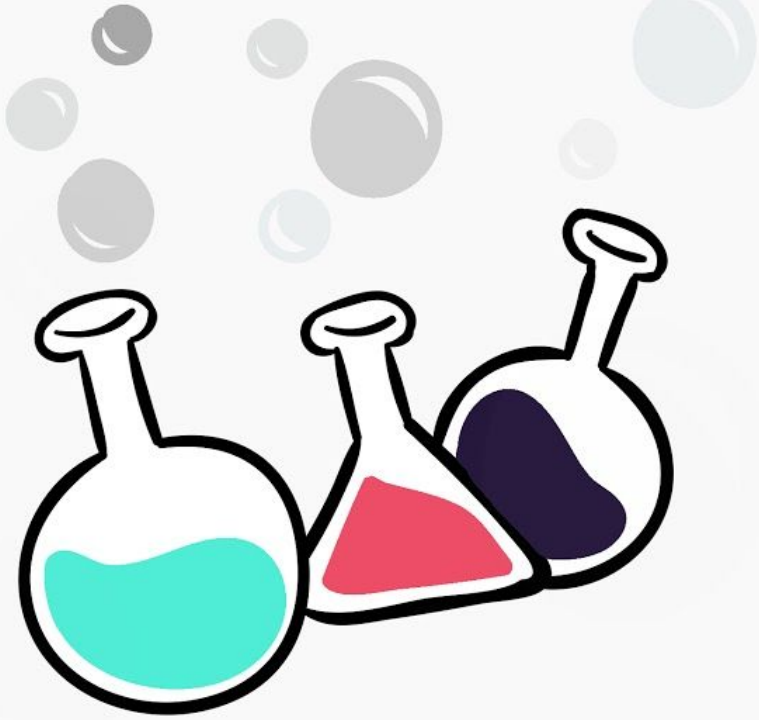

ORGANOPHOSPHATES

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[Color index : Important | Notes | Extra | Editing file]

Introduction to Pesticides

- **What is it?**

Pesticides is a generic term used to refer to all pest-killing agents and they include:
-Insecticides (substances used to kill insects, most commonly used pesticides, most are organophosphates)
-Herbicides (chemical substances used to control unwanted plants, weedkillers)
-Rodenticides (chemicals made and sold for the purpose of killing rodents, rats, and Anticoagulant Rodenticides like
:warfarin , second most commonly used pesticides)
-Fungicides (biocidal chemical compounds or biological organisms used to kill parasitic fungi or their spores)
- Fumigants (used to control pests in buildings)
Many are general protoplasmic poisons affecting a wide range of organisms, including humans.

Two common types	
1-ORGANOPHOSPHATES	2-CARBAMATE INSECTICIDES

ORGANOPHOSPHATES

❖What is it?

-Organophosphates are highly lipid soluble substances that are readily absorbed via dermal, GI, and respiratory routes on long duration
-The lipid solubility property **results in its storage in body fat**, making toxic systemic levels possible from gradual or rapid accumulation from repeated low-level exposures and the patient may represent as an acute or a chronic case

❖Pathophysiology

-Organophosphates 'the parent compound' and its metabolites are acetylcholinesterase inhibitors (AChEI) (the enzymatic deactivator of acetylcholine toxicity in farmers and anti-lice shampoo mostly in children usually at end of summer before school)
-Inhibition occurs mainly at tissue sites (true acetylcholinesterase represented by erythrocyte cholinesterase) and in plasma (circulating pseudocholinesterase)

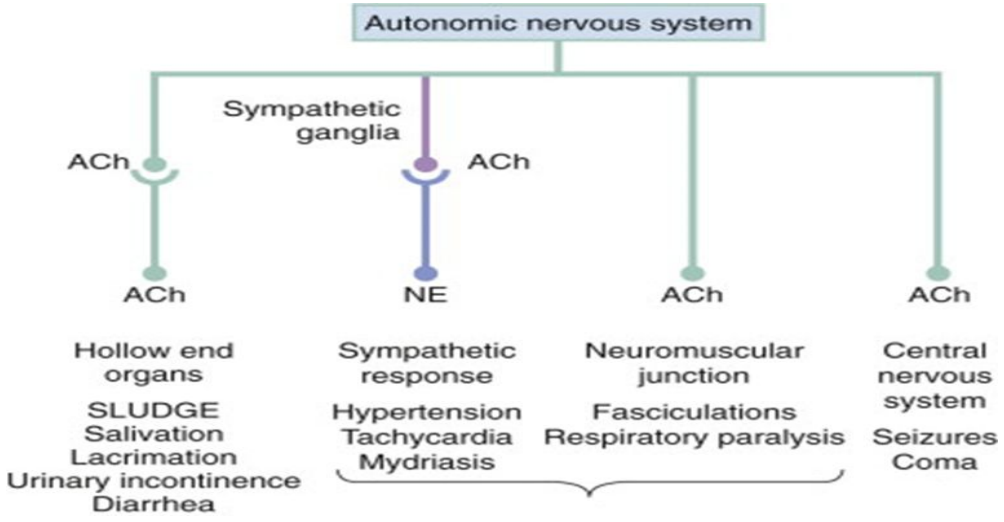
- **Because of the inhibition of the AChE, acetylcholine ↑ at receptors located in:**
  - Sympathetic & parasympathetic Ganglion (Nicotinic sites)
  - Postganglionic Cholinergic sympathetic and parasympathetic (Muscarinic sites)
  - Skeletal muscle (Nicotinic sites)
  - Central nervous system sites

- **In the sympathetic nervous system (thoracolumbar outflow 'from T1 to L2'):**

The neurotransmitter in ganglia is acetylcholine (ACh) in the target organ it is norepinephrine (NE).

- **Parasympathetic nervous system (craniosacral outflow):**
  Uses ACh as the neurotransmitter in preganglionic and postganglionic target organs.
  -The ANS is divided further into the Muscarinic and Nicotinic receptors, Atropine can block Muscarinic receptors but not Nicotinic receptors "atropine can thus reverse almost all symptoms except respiratory paralysis > either wait and support the patient or give pralidoxime"
  -In the brain, ACh is just one of several active neurotransmitters

  -Many of the parent compounds are less potent than its metabolites and this may result in delayed onset of toxicity (Parathion to Paraoxon)



❖ Clinical features

- **Symptoms:** mostly muscarinic, less nicotinic
  -The accumulation of ACh results in a classic cholinergic syndrome, manifested by hyperactivity of cholinergic responses
  -Muscarinic AChE inhibition is commonly called the SLUDGE syndrome or DUMBELS: patient is leaking from every body orifice (MCQs:)

Salivation	Diarrhea/Diaphoresis
Lacrimation	Urination
Urinary incontinence	Miosis rarely mydriasis can happen
Defecation	Bradycardia/Bronchorrhea/Bronchospasm
Gastrointestinal cramps	Emesis
Emesis	Lacrimation Salivation

- **Signs:**

- wheezing and crepitation due to hyper salivation

-Bradycardia is a classic sign of the cholinergic syndrome, but the increased release of norepinephrine from postganglionic sympathetic neurons may result in normal or even tachycardia heart rates (nicotinic effect).

Tachycardia is due to 1- sympathetic activity 2- dehydration

-**CNS:** A combination of involvement of the N-methyl-d-aspartate (NMDA) receptor and enhanced acetylcholine concentrations can lead to seizures

-**NMJ:** excess acetylcholine causes hyper stimulation of the muscles with secondary paralysis

The usual clinical picture of acute organophosphorus poisoning is impressive (SLUDGE), while toxicity from gradual, cumulative exposure may be much more subtle manifesting as vague confusion or other central nervous system complaints, mild visual disturbances, or chronic abdominal cramping, nausea, and diarrhea

Acute poisoning is more common

❖Diagnostic strategies

-Toxicity confirmed by ordering plasma and RBC cholinesterase levels

-**In acute exposures**, the plasma cholinesterase levels decrease first, followed by decreases in RBC cholinesterase levels

-The RBC cholinesterase level is more indicative of what is occurring at the nerve terminal

-**Patients with chronic exposures** may show only reduced RBC cholinesterase activity, with a normal plasma cholinesterase level (MCQ).

-RBC cholinesterase levels recover at a rate of 1% per day in untreated patients and take approximately 6 to 12 weeks to normalize, whereas plasma cholinesterase levels may recover in 4 to 6 weeks.

-Other studies should focus on the evaluation of pulmonary, cardiovascular, and renal function and fluid and electrolyte balance.

-Patients presenting with no acidosis, or only a metabolic acidosis on the arterial blood gas, have lower mortality than those presenting with a respiratory or mixed acidosis

Atropine is also used for diagnosis, the likelihood of organophosphate poisoning is greatly increased if few or none of the following features are seen after administering atropine: dry skin and mucous membranes, increased heart rate, moderately dilated pupils, and decreased bowel sounds.

❖ Management

- **Aim of management:**

1- Decontamination 2- Supportive care (ABC) 3- Reversal of ACh excess at muscarinic sites (Atropine) 4- Reversal of toxin binding at active sites on the cholinesterase molecule (Pralidoxime)

Decontamination:

-Decontamination is particularly important in cases of dermal exposure; removal and destruction of clothing and thorough flushing of exposed skin may limit absorption

- Caregivers are at risk from splashes or handling of contaminated clothing.

- Should use universal precautions:new studies show no need to shave hair,just shower with soap &water

-Military resins, flour, sand or bentonite for dermal decontamination

-The individuals decontaminating should take great care when handling exposed articles of clothing

-In the case of ingestion, decontamination isn't that beneficial

why can't we use activated charcoal ?
1- organophosphates are lipid-soluble > quickly absorbed from the GI 2- Nausea and vomiting
The ingested dose in fatal cases could be too large for the amount of charcoal given, the charcoal might be given too late, or the solvent might interfere with binding. No evidence suggests that patients with pesticide poisoning benefit from treatment with activated charcoal

Supportive care:
-(ABC) Airway management, Breathing and Circulation
-Airway management includes suctioning of secretions and vomitus, oxygenation and when necessary, intubation and ventilatory support
-Intravenous access and fluid boluses as needed for circulatory collapse
-Seizure/Convulsions can be controlled by Benzodiazepine

Reversal of ACh excess at muscarinic sites:
-Atropine (definitive treatment) can be used as a competitive inhibitor of acetylcholine at muscarinic receptor sites, atropine reverses the clinical effects of cholinergic excess at parasympathetic end organs and sweat glands
-Large doses of atropine may be required and the faster the atropinization the better
Suggested dosing is 1 or 2 mg of atropine IV, until there is control of mucous membrane hypersecretion and the airway clears.
-If IV access is not immediately available, atropine may be administered IM
-Tachycardia and mydriasis may occur at these doses, but they are not indications to stop atropine administration. as the half life of atropine is shorter than the half life of organophosphates, initial improvement doesn't necessarily indicate resolution of toxicity until secretions dry.
-The endpoint of atropinization is drying of respiratory secretions, easing of respiration, and a mean arterial pressure greater than 60 mmHg
-Atropine is not active at nicotinic sites and does not reverse the skeletal muscle effects > pralidoxime

Reversal of toxin binding at active sites on the cholinesterase molecule:
-AChE inhibition treatment is the use of an Oxime:
- Pralidoxime (2-PAM, Protopam)
- Obidoxime (Toxigonin)

-These degrade the organophosphate-AChE complex and restore cholinesterase activity at muscarinic and nicotinic sites
-The medication may be given as repeated boluses or continuous infusion the infusion may need to be continued for several days for complete reversal of cholinesterase activity

-Indications for oxime therapy include:
1-respiratory depression/apnea
2-fasciculations
3-seizures
4-arrhythmias, cardiovascular instability
5-Patients who need large amounts of atropine (2–4 mg) to completely reverse the signs and symptoms of intoxication
6-patient who requires repeated doses of atropine

❖ Disposition

-Most patients with significant exposures require hospital admission including intensive care settings
-A person with chronic exposure, and mild visual or GI symptoms may be followed as outpatient
-Asymptomatic or mildly symptomatic patients with near normal cholinesterase levels may be discharged after 4 to 6 hours

- The intermediate syndrome (IMS), occurs 24 to 96 hours after exposure and consists of proximal muscular weakness specifically of the respiratory muscles. It is believed to be an abnormality at the neuromuscular junction. Patients with IMS present with respiratory failure several days after the acute cholinergic symptoms have resolved and may require several weeks of ventilatory support. self-limiting
- Organophosphorus-delayed neuropathy affects an axonal enzyme, neurotoxic esterase, and leads to a peripheral sensorimotor neuropathy 7 to 21 days after exposure. it is self-limiting

❖ Complications

-Seizure, bronchorrhea and bronchoconstriction are prominent mechanisms of early morbidity
-Obstruction of upper and lower airways produce hypoxia
-Muscle hyperactivity eventually gives way to muscle paralysis 'secondary paralysis' (including respiratory muscles and diaphragm)leading to respiratory arrest.
-Respiratory insufficiency results in death if not anticipated and corrected
-Unique effect of Organophosphates results from "aging"[1] will occur by 48 hours, but may take longer, the irreversible structural change that occurs in cholinesterase enzyme when the organophosphorus agent is bound to it for a prolonged time and these changes can't be reversed with oximes

CARBAMATE INSECTICIDES

-Carbamate insecticides are another class of acetylcholinesterase inhibitors and are differentiated from the organophosphorus compounds by their relatively short duration of toxic effects. Carbamates inhibit acetylcholinesterase for minutes to 48 hours, and the carbamate-cholinesterase binding is reversible (No "Aging" process on the enzyme)
-Although the clinical picture is nearly identical to that of organophosphate toxicity, usually patient would require simple decontamination, supportive care and an adequate dose of atropine, plus the use of Oxime in this case is controversial, because when using Oxime all you're aiming for is to reverse the toxin binding at active sites on the AChE enzyme to try and prevent the aging process on the enzyme however, with Carbamate insecticides the toxicity has a short duration and its binding to the enzyme is reversible.
In severe cases, ventilator and seizure therapy is required.

[1] Progressive inhibition of cholinesterases by organophosphates results from phosphorylation of the active-site serine. Phosphorylated cholinesterases may undergo a dealkylation reaction of the organophosphorus moiety leading to "aged" enzyme

Take home message

Pesticides: ORGANOPHOSPHATES and CARBAMATE INSECTICIDES
-Both inhibit AChE, but Carbamate Insecticides have shorter duration and they are reversible (No "Aging" process on the enzyme)

Organophosphates:
-Lipid soluble compounds that block the AChE leading to an increase of ACh levels at tissue and plasma sites, (Muscarinic sites) and (Nicotinic sites)
-Symptoms are summarized with SLUDGE and DUMBELS
-Signs Bradycardia or tachycardia, Seizures, Hyperstimulated muscles
-Diagnosis mainly plasma and RBC cholinesterase levels
-Management:
-Decontamination with military resins, flour, sand or bentonite for dermal decontamination
-ABCs
-Atropine for the reversal of ACh excess at muscarinic sites
-Oxime for the reversal of toxin binding at active sites on the cholinesterase
-Complications:
Seizures
Hypoxia
Paralysis
Respiratory insufficiency

Carbamate Insecticides:
-Decontamination and Atropine are usually enough, Ventilator and seizure therapy is only used in severe cases.

MSQs

1-Neuro terminal activities in organophosphate toxicity will be identified through?
A. Acetylcholine levels in the blood.
B. Acetylcholinesterase levels in the blood
C. Dopamine levels in CSF
D. Adrenaline levels in the blood
Ans: B

2-Which of the following neuro-receptors is responsible in organophosphate positioning?
A.Adrenergic receptor
B.Muscarinic receptor
C.Dopaminergic receptor
D.Nicotinic receptor
Answer: B

3-Inhibition of Acetylcholinesterase leads to which one of the following signs & symptoms?
A. Cholinergic
B. Anticholinergic
C. Sympathomimetics
D. Sympatholytic
Ans: A

4-A 40 year old farmer called an ambulance, as he was unwell having diarrhea and vomiting. He finished spraying his crops with pesticide same day. As he arrives in hospital you notice that patient has excessive salivation, lacrimation and miosis. Which toxidrome this patient has?
A. Organophosphorus
B. Sympathomimetic
C. Opioid
D. Sedative
Answer: A

5-In which way is the mechanism of organophosphate and carbamate insecticides similar?
A. They activated acetylcholinesterase
B. They produce anticholinergic syndrome
C. They both respond to atropine
D. They both respond to Oximes
Ans: C

6-What is the Mechanism of the action of pralidoxime?
A.It degrades the bond between the poison and acetylcholinestrase
B.It provides new acetylcholinestrase
C.It increase the concentration of acetylcholine by 50%
D.It increase the concentration of acetylcholinestrase by 50%
Answer: A

7-Which one of the following is the characteristic of "aging" in organophosphorus poisoning?
A- There is no bond between the poison and acetylcholinesterase
B-All the acetylcholinesterase is consumed by the poison
C-The body cannot synthesize any more acetylcholinesterase
d. The bond between the poison and acetylcholinesterase is irreversible
Answer: D

8-Which one of the following is the antidote for organophosphorus poisoning?
A- Atropine
B-Calcium gluconate
C-Potassium chloride
D- Hyoscine
Answer: A