



CHOLINESTERASE INHIBITORS

(Pesticides)

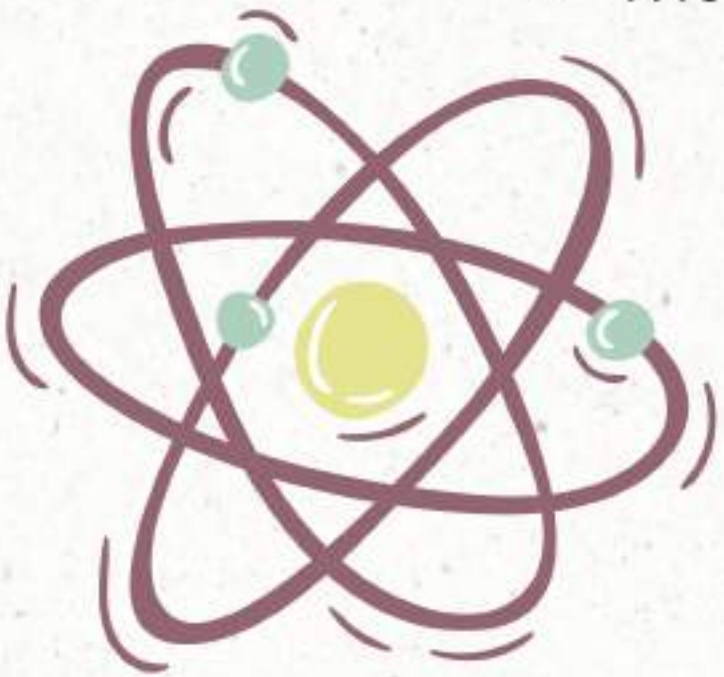
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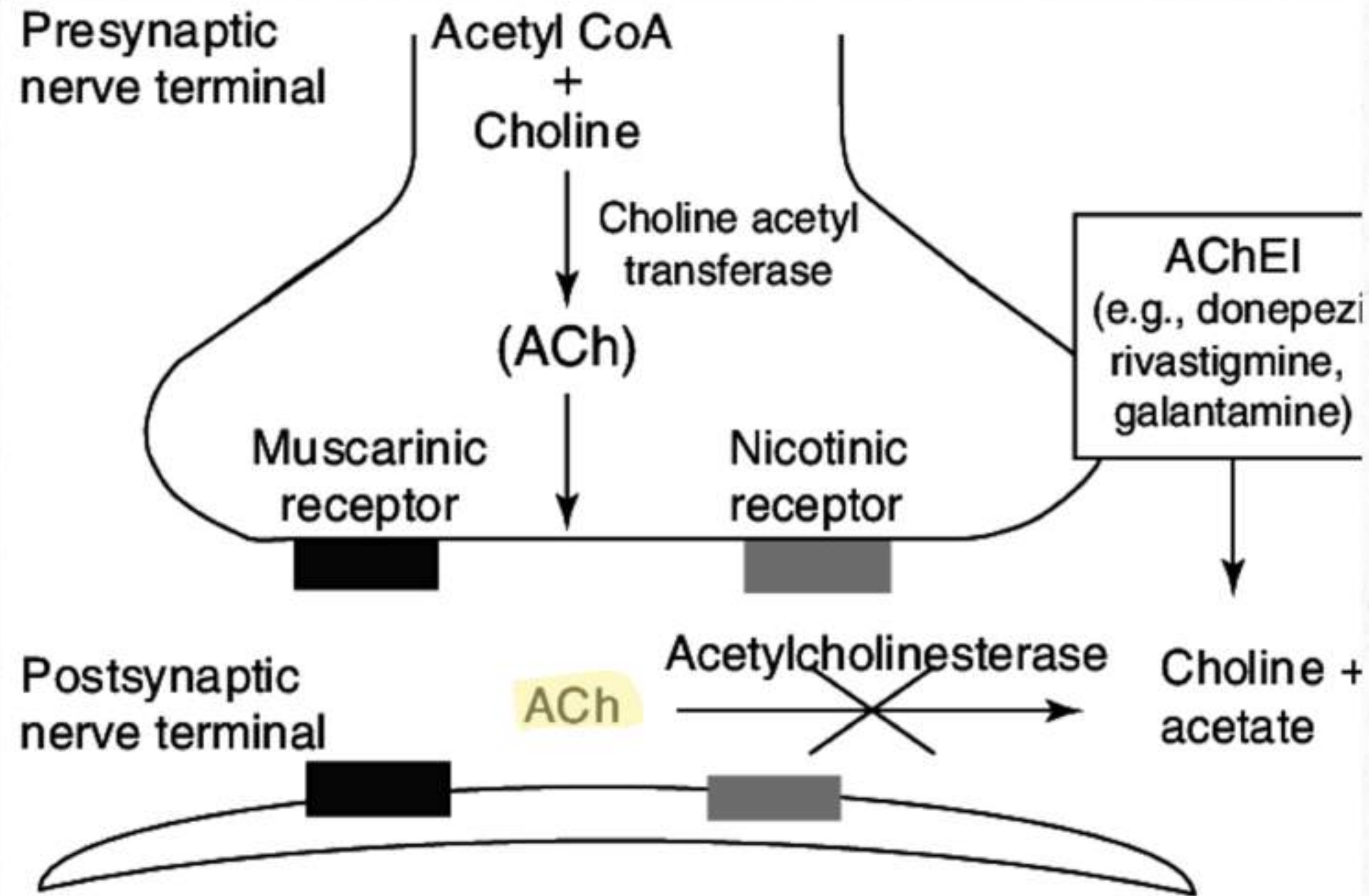


OUTLINES

- definition ,mechanism of action ,uses ,side effects of Cholinesterase
- Inhibitors .
- Introduction to pesticides.
- introduction to cholinesterase inhibitors pesticides .
- clinical presentation and clinical investigation.
- management and medications.



what are cholinesterase inhibitors?





CHOLINESTERASE INHIBITORS



- Cholinesterase inhibitors (ChEIs), also known as **anti-cholinesterase**, are chemicals that prevent the breakdown of the neurotransmitter acetylcholine or butyrylcholine. This increases the amount of the acetylcholine or butyrylcholine in the synaptic cleft that can bind to muscarinic receptors, nicotinic receptors and others. Thus, symptoms of **overstimulation of the parasympathetic** nervous system, such as increased hypermotility, hypersecretion, bradycardia, miosis, diarrhea, and hypotension.

This group of inhibitors is divided into:

1. acetylcholinesterase inhibitors (AChEIs)
2. butyrylcholinesterase inhibitors.

. ChEIs may be used as drugs for **Alzheimer's** and **myasthenia gravis**, and also as **chemical weapons** and **insecticides**.

Side effects when used as drugs may include :

Loss of appetite, nausea, vomiting, loose stools, vivid dreams at night, dehydration, rash, bradycardia, peptic ulcer disease, seizures, weight loss, rhinorrhea, salivation, muscle cramps, and fasciculations.





CHOLINESTERASE INHIBITORS



- ChEIs are **indirect-acting** parasympathomimetic drugs.
- ChEIs are widely used as **chemical weapons**. Since November 2019 the group of AChEIs known as Novichoks have been banned as agents of warfare under the Chemical Weapons Convention. Novichok agents are neurotoxic organophosphorus compounds and are considered more potent than VX gas

CHOLINESTERASE INHIBITORS

Acetylcholinesterase Inhibitors for Discussion		
<u>Reversible Inhibitors</u>	<u>Irreversible Inhibitors</u>	<u>Centrally Targeted Inhibitors</u>
Physostigmine Salicylate (P)	Sarin [warfare agent]	Rivastigmine Tartrate (Exelon)
Pyridostigmine Bromide	Malathion [insecticide]	Donepezil HCl (Aricept)*
Edrophonium Chloride		Galantamine HBr
Neostigmine Methylsulfate	<u>Antidote</u>	
	Pralidoxime Chloride	
*P = Prototype Drug; *Drug with Brand/Generic Importance		

CHOLINESTERASE INHIBITORS

- For the treatment of [Alzheimer's Disease](#) and [dementia](#) we can use from 3 CHEIs Which are [rivastigmine](#), [donepezil](#), and [galantamine](#).
- If a benefit occurs, it is generally during the second or third month after starting.
- It is difficult to determine which ChEI has greater efficacy, due to design flaws in head-to-head comparison studies.
-
- [Pyridostigmine](#) is used in the treatment of [myasthenia gravis](#).
- [Neostigmine](#) is used in combination with a [muscarinic antagonist](#) to reverse the effects of non-depolarizing muscle relaxants e.g. [rocuronium bromide](#)



PESTICIDE

Pesticide :any substance or mixture of substances intended for preventing, destroying,repelling,or mitigating any pest.

A pest is any harmful,destructive,or troublesome animal,Loading...plant or microorganism.

The Organic Phosphorus Compound “OPC” are now the largest and most versatile class of insecticides

Any pesticide that can bind,or inhibit,cholinesterase,making it unable to breakdown acetylcholine,is called a "cholinesterase inhibitor," or "anticholinesterase agent” Which produces a state of acetylcholine excess .

The resulting excessive cholinergic activity produces severe secretions from many sites , stimulation of smooth muscle and inhibition of nerve transmission in skeletal muscle; this affects respiratory muscles and causes respiratory failure . Human exposure to cholinesterase inhibiting chemicals can result from inhalation, ingestion,or eye or skin contact





PESTICIDE



TWO MAIN CLASSES OF CHOLINESTERASE INHIBITING (PESTICIDES)

ORGANOPHOSPHATES (OPS)

- Parathion
- Malathion
- Diazinon
- Chlorpyrifos
- Disulfoton
- Azinphos-methyl

CARBAMATES (CMS)

- Aldicarb
- Bendiocarb
- Bufencarb
- Methomyl (Lannate, Nudrin) CHOLINESTERASE



PESTICIDE

Organophosphate insecticides include some of the most toxic pesticides. They can enter the human body through skin absorption, inhalation and ingestion. They can affect cholinesterase activity in both red blood cells and in blood plasma, and can act directly, or in combination with other enzymes, on cholinesterase in the body.



what is the difference between OPCS and CM ?

The main difference in the mechanism of action between OPCs and CM is that CMs spontaneously hydrolyze from the AChE site within 24 hours, whereas OPCs undergo aging.

- Aging occurs when the phosphorylated AChE nonenzymatically loses an alkyl side chain, becoming irreversibly inactivated. Carbamates, however, reversibly bind to the active site and do not undergo aging.



PESTICIDE



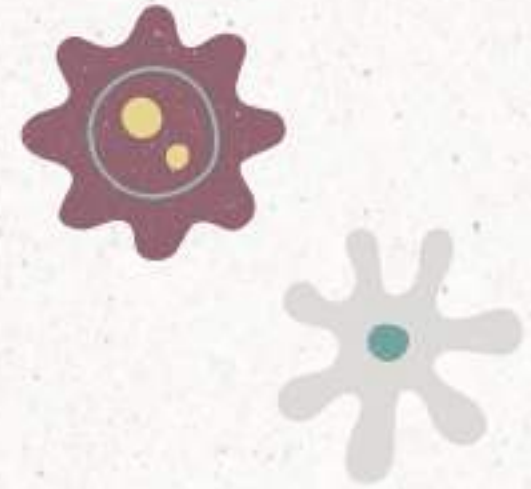
WHAT HAPPENS AS A RESULT OF OVEREXPOSURE TO CHOLINESTERASE INHIBITING PESTICIDES?

Overexposure can result in cholinesterase inhibition. These pesticides combine with acetylcholinesterase at nerve endings in the brain and nervous system, and with other types of cholinesterase found in the blood. This allows acetylcholine to build up, while protective levels of the cholinesterase enzyme decrease.





CHOLINESTRASE INHIBITORS (PESTICIDE)



Illness Associated with Cholinesterase Inhibitors and Pesticides

Acute illness due to cholinesterase inhibition manifests with symptoms and signs resulting from toxic effects on the **central and peripheral nervous system**.

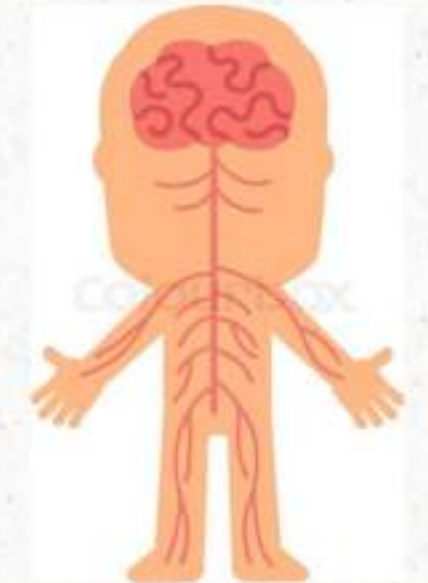
Central nervous system (CNS) symptoms and signs :

confusion, headache, loss of consciousness, and, in severe overexposures, death due to respiratory center depression.

Peripheral symptoms and signs:

salivation, lacrimation, blurry vision, excessive bronchial secretions, sweating, weakness, muscle fasciculations, diarrhea, and loss of bladder control.

Severe cholinesterase inhibition can result in death primarily because of respiratory failure. This failure results from a combination of bronchial secretions, bronchial constriction, weakened respiratory muscle function, and inhibited respiratory drive.





CHOLINESTRASE INHIBITORS (PESTICIDE)



PHARMACOKINETICS

Absorption :rapidly and well absorbed from the skin,conjunctiva,GI tract,and lungs.

Distribution : most are polar, water-soluble chemicals, but a few compounds possess high-partition coefficients (e.g. Dichlofenthion), which may lead to delayed, prolonged symptoms.

Elimination :detoxified by Cytochrome P450-mediated monooxygenases in the liver.

- Some metabolites are more toxic than parent compounds and they are usually detected from 12 to 48 hours postexposure.





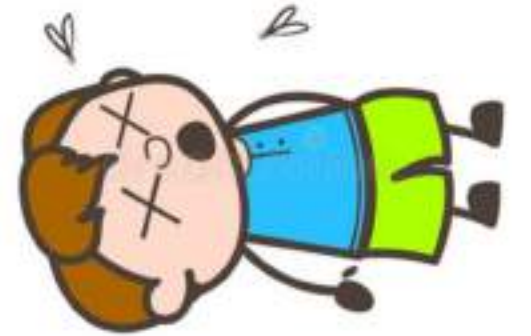
CHOLINESTRASE INHIBITORS (PESTICIDE)



TOXIC DOSE ☠️

Toxic signs and symptoms appear when the **cholinesterase level drops to 30 %** of its normal activity.

- Fatalities begin to occur after the ingestion of 125-175 mg.
- Death can occur in less than an hour after ingestion.



MORTALITY 🚰

Worldwide mortality studies report mortality rates from 3- 25%.The compounds most frequently involved include Malathion,Dichlorvos,Trichlorfon, and Fenitrothion.

- Mortality rates depend on the Type of compound used, Amount ingested, General health of the patient, Delay in Discovery and transport, Insufficient respiratory Management, and Delay in intubation.
- **RESPIRATORY FAILURE is the most common cause of death.**



CLINICAL PRESENTATION

- **Signs and symptoms of cholinesterase inhibition from exposure to CMs or OPs** include the following:
 - **In mild cases** (within 4 - 24 hours of contact): tiredness, weakness, dizziness, nausea and blurred vision;
 - **In moderate cases** (within 4 - 24 hours of contact): headache, sweating, tearing, drooling, vomiting, tunnel vision, and twitching;
 - **In severe cases** (after continued daily absorption): abdominal cramps, urinating, diarrhea, muscular tremors, staggering gait, pinpoint pupils, hypotension (abnormally low blood pressure), slow heartbeat, breathing difficulty, and possibly death, if not promptly treated by a physician.
- **Symptoms develop several hours post exposure, but symptoms can occur 5 minutes after massive ingestions.**
 - Oral or Respiratory exposures :S&S within 3 hours.
 - Dermal absorption:S&S may be delayed up to 12 hours.
 - If symptoms begin after more than 24 hours:Acute organophosphate poisoning is equivocal. This exceptions are highly lipid-soluble compounds, which can cause mild initial symptoms followed by cholinergic crisis in 40 to 48 hours. Miosis is the most constant sign, but its absence does not exclude organophosphate poisoning.
 - Muscle fasciculation are a highly reliable sign.





CLINICAL PRESENTATION



The types and severity of cholinesterase inhibition symptoms depend on:

- (a) the toxicity of the pesticide.
- (b) the amount of pesticide involved in the exposure.
- (c) the route of exposure.
- (d) the duration of exposure.





CLINICAL PRESENTATION



Although the signs of cholinesterase inhibition are similar for both carbamate and organophosphate poisoning, **blood cholinesterase returns to safe levels much more quickly after exposure to CMs than after OP exposure**. Depending on the degree of exposure, cholinesterase levels may return to pre-exposure levels after a period ranging from several hours to several days for carbamate exposure, and from a few days to several weeks for organophosphates.

- When symptoms of decreased cholinesterase levels first appear, it is impossible to tell whether a poisoning will be mild or severe. In many instances, when the skin is contaminated, symptoms can quickly go from mild to severe even though the area is washed. Certain chemicals can continue to be absorbed through the skin in spite of cleaning efforts.





CLINICAL PRESENTATION



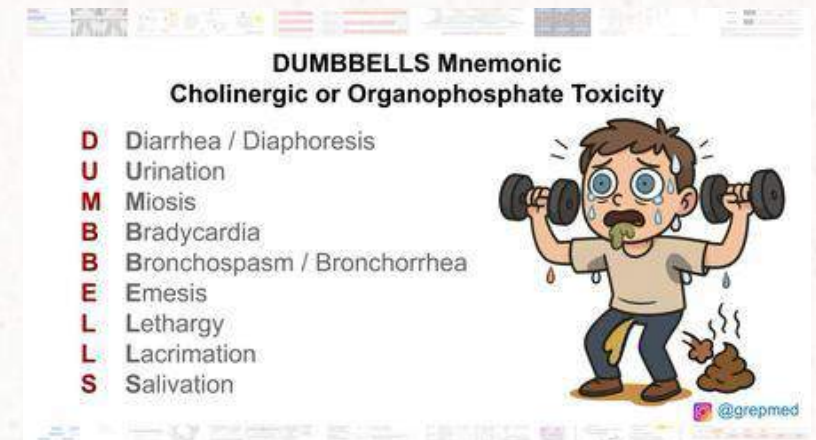
Several factors should be considered in deciding how often someone should have his/her cholinesterase levels tested:

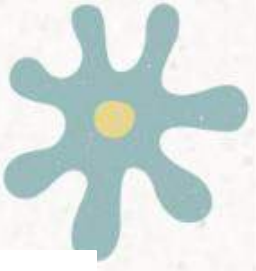
- a) The extent and seriousness of the possible exposure. This will vary with the toxicity of the pesticides being used and how often they are handled.
- b) The type of work being done and the equipment being used may involve different risks of exposure.
- c) Work practices have an important effect on worker safety. Some good practices include: the proper use of protective clothing and equipment; showering after each job; avoidance of drinking, eating and smoking in pesticide contaminated areas; prompt and effective decontamination in the event of spills.
- d) The past safety record of a company and the work history and experience of an individual.
- e) The physician's experience and familiarity with a specific work force may be an additional factor





- **A)cholinergic Toxidrome (3 sets of sign and symptoms) =Acute phase**
- Due to accumulation of ACh at three sites :
- At postganglionic muscarinic synapses leads to Parasympathetic activity of smooth muscle and increased activity in postganglionic sympathetic receptors for sweat glands. This results in the symptoms and signs that can be remembered with the mnemonic **SLUDGE/DUMBELS**
- At nicotinic motor end plates causes persistent depolarization of skeletal muscle (analogous to that of succinylcholine), resulting in fasciculation, progressive weakness, hypotonicity, hypertension, tachycardia, and pallor.
- As OPs cross the blood-brain barrier, they cause anxiety, emotional instability, restlessness, confusion, ataxia, tremors, seizures, and coma.





B) Intermediate Syndrome

- Timing: 24-96 hours after exposure.
- What is it? Weakness of neck, trunk, proximal muscles, and respiratory muscles with relative sparing of distal muscle group
- The Danger: Potentially lethal respiratory failure after the patient seemed to improve.

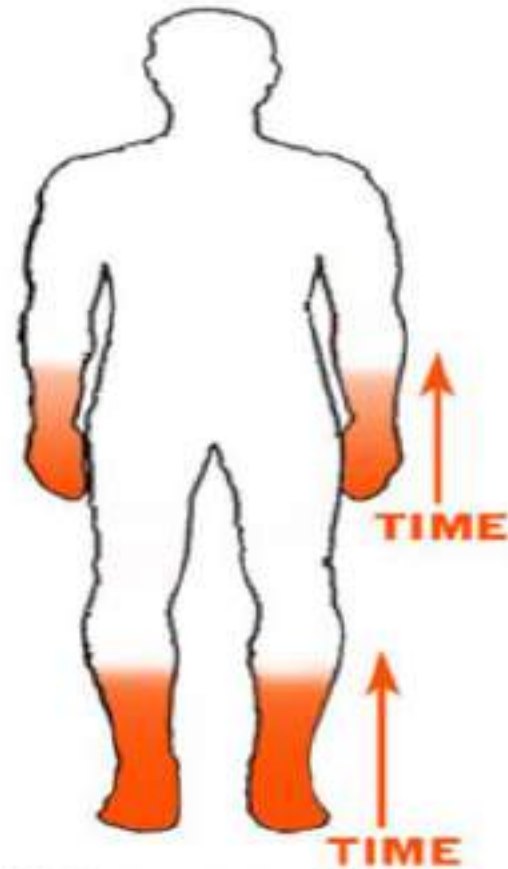
C) Organophosphate –induced delayed neuropathy OPIDN

Timing : 1-3 weeks later

- Affected patients present with transient, painful “**stocking-glove**” paresthesia followed by a **symmetrical motor poly-neuropathy** characterized by flaccid weakness of the lower extremities, which ascends to involve the upper extremities.
- Sensory disturbances are usually mild. Delayed neurotoxicity primarily affects distal muscle groups, but in severe neurotoxicity, proximal muscles groups may also be affected.
- **Note :** The risk of developing OPIDN is not related to the severity of the initial cholinergic poisoning.

Some potent cholinergic agents (e.g., parathion) do not cause OPIDN .Conversely, some agents (e.g., TOCP) cause little cholinergic illness but are known to cause OPIDN.

“STOCKING-GLOVE” PARESTHESIA



Polyneuropathy
First symptoms on
toes and feet. Later
Stocking-gloves pattern



• DIAGNOSIS & INVESTIGATION

- Some of the above symptoms can be confused with influenza (flu), heat prostration, alcohol intoxication, exhaustion, hypoglycaemia, asthma, gastroenteritis, Acute Respiratory Distress Syndrome (ARDS), pneumonia, and brain haemorrhage.
- A good history (e.g., farmer, smell of pesticides on clothes) is crucial to avoid misdiagnosis.
- The diagnosis of cholinergic toxicity is a clinical diagnosis. It is based on the patient's history, signs and symptoms. Lab tests come later to confirm and guide management, but they **MUST NOT** delay treatment."
- **Treatment should NEVER wait for lab results!**

1. Cholinesterase Levels

This is the core lab test

Feature	RBC Acetylcholinesterase	Plasma (Butyryl) Cholinesterase
What does it measure?	The enzyme found in neurons & red blood cells	An enzyme produced by the liver & found in plasma
Diagnostic Importance	More Accurate - better reflects nervous system inhibition	Faster & Easier to assay
Best Used For	Assessing chronic exposure & long-term follow-up	Detecting acute poisoning
Important Pitfalls	-	Levels affected by pregnancy, infection, and medical illness

- Normal ranges of RBC and serum cholinesterase vary widely between individuals.
- "A low Plasma Cholinesterase is a strong sign of poisoning. But remember: A severely poisoned patient could still have a 'low-normal' level if their baseline was very high!"
- The point at which various authors have suggested that toxicity begins to appear ranges from 40% to 75% of normal values

2. Recommended Studies:

- CBC, Glucose, BUN, Electrolytes
- Prothrombin Time, Liver Function Studies, Amylase
- Common Findings:
 - Leukocytosis and Hemoconcentration
 - Acidosis (Metabolic and/or Respiratory)
 - Electrolyte Imbalance: Hyperglycemia, Hypokalemia, Hypomagnesemia
 - Elevated Amylase and Liver Enzymes
- Note:
 - Pretreatment metabolic/respiratory acidosis directly correlates with severity of poisoning and mortality.



3. Electrocardiogram (ECG):

- Most Common: Prolonged QT interval
- Common Arrhythmias: Sinus Tachycardia and Sinus Bradycardia (equally frequent)
- Rare Findings: ST-segment elevation, complete heart block

4. Chest X-Ray: May show pulmonary edema, but has limited impact on clinical management.



- **Initial management :**
- **Decontamination :**

The 1st priority in managing patients is to prevent secondary exposure and injury to others in their proximity because of contaminated skin, clothing, hair, or emesis.

Remove contaminated clothing and wash the skin thoroughly with soap and water, while protecting responders with personal protective equipment (PPE).

Irrigate the eyes of patients who have had ocular exposure using isotonic sodium chloride solution or lactated Ringer's solution Morgan lenses can be used for eye irrigation.

- **Secure Airway :**

Moderately to severely poisoned patients with markedly depressed mental status require 100% oxygen and immediate endo-tracheal intubation

Airway control and adequate oxygenation are essential in cholinergic toxidrome.

Intubation may be necessary in cases of respiratory distress due to laryngospasm, bronchospasm, bronchorrhea, or seizures.

Immediate aggressive use of atropine may eliminate the need for intubation.

❖ Data is lacking to show that any of the following treatments improve the outcome in poisoned patients: Activated charcoal, Cathartics (laxatives), Gastric lavage, Syrup of ipecac (induce vomiting)



Pharmacological treatment :

1. Atropine:

MOA:

competes with acetylcholine at muscarinic receptors, preventing cholinergic activation

Dose:

- For moderate to severe cholinergic toxicity, atropine should be administered beginning at a dose of 2 to 5 mg IV for adults and 0.05 mg/kg IV for children. If no effect is noted the dose should be doubled every three to five minutes until pulmonary muscarinic signs and symptoms are alleviated.
- Atropine dosing should be titrated to the therapeutic end point of the clearing of respiratory secretions and the cessation of broncho-constriction.
- Tachycardia and mydriasis are NOT appropriate markers for therapeutic improvement as they may indicate continued hypoxia, hypovolemia, or sympathetic stimulation•
- In patients with severe poisoning, HUNDREDS of milligrams of atropine by bolus and CONTINUOUS INFUSION may be required over the course of SEVERAL DAYS.

Contraindication :

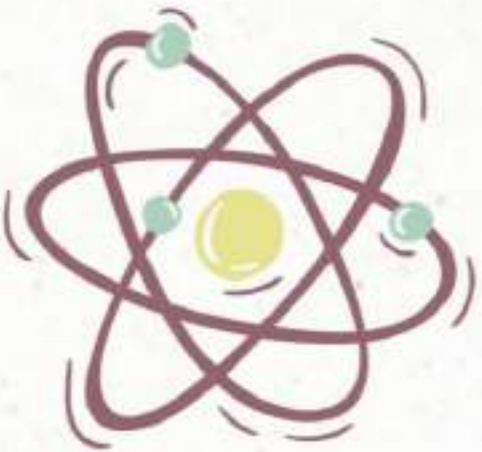
Documented hypersensitivity and narrow- angle glaucoma .

Side effects :

- Blurred vision. • Dry mouth. • Inability to sweat. • Muscle fasciculations. • Mydriasis. • Paralytic ileus • Pyrexia.
- Tachycardia

- **Note:**

Atropine is the only antidote needed to treat cholinesterase inhibition resulting from carbamate exposure, as carbamates bind to acetylcholinesterase reversibly .



2. Pralidoxime (2-PAM, Protopam)



- **MOA:**

2-PAM attaches to cholinesterase inhibitors that have blocked cholinesterase and removes them from the enzyme, thereby reactivating it.

- Some cholinesterase inhibitors after a time will form a permanent bond (Aging), after which 2-PAM is no longer effective. Aging occurs in the phosphorylated enzyme bond within 2 min-12 hrs.
- Since atropine does not bind to nicotinic receptors, it is ineffective in treating neuromuscular dysfunction. Pralidoxime (2-PAM) and other oximes, such as HI-6 and obidoxime, are cholinesterase reactivating agents that are effective in treating both muscarinic and nicotinic symptoms.
- Pralidoxime should NOT be administered Without concurrent atropine in order to prevent worsening symptoms due to transient oxime-induced acetylcholinesterase inhibition.
- Current recommendation is administration within 48 h of OP poisoning.

- **Dose:**

- The current WHO recommendation for IV bolus therapy with pralidoxime is at least 30mg/kg in adults, and 25 to 50 mg/kg for children, based upon the severity of symptoms.
- Pralidoxime should be administered slowly over 30 minutes, since rapid administration has occasionally been associated with cardiac arrest, and slow administration prevents the muscle weakness that results from the transient inhibition of acetylcholinesterase as pralidoxime binds to the enzyme
- After the bolus dose, it appears that superior antidotal effects occur with pralidoxime given as a continuous infusion of at least 8 mg/kg per hour in adults and 10 to 20 mg/kg per hour for children.

- **Side effect:**

- 2-PAM can cause brief adverse effects such as dizziness and blurred vision; hypertension may occur (increasing infusion time to 30-40 min can help reduce this effect).

3. Diazepam (Valium, Diastat, Diazemuls)

- Used for treatment of seizures.

- **MOA:**

Depresses all levels of CNS by increasing activity of GABA.

- Prophylactic diazepam has been shown to decrease neuro-cognitive dysfunction after organophosphorus agent poisoning .
- This led, in part, to the US military development of a 10 mg auto-injector of diazepam for use in the setting of chemical attack

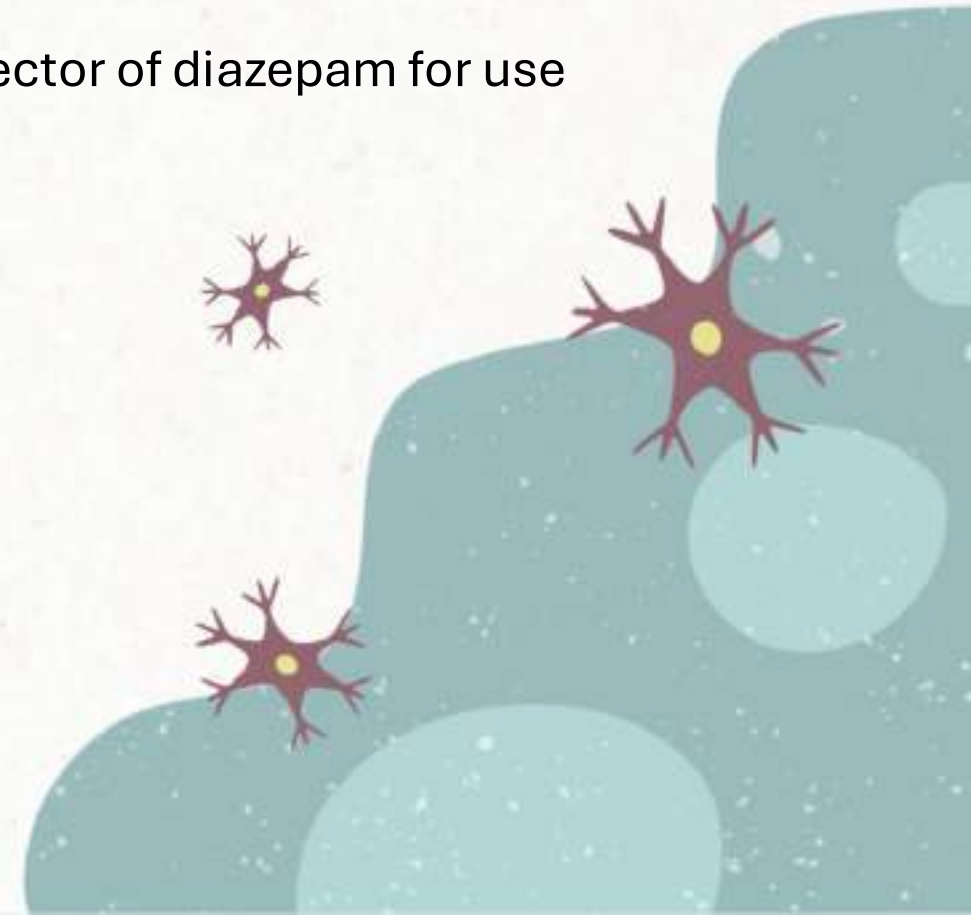
Dosing:

Adult:

5-15 mg IV q5-10 min, repeat; consider higher doses if needed.

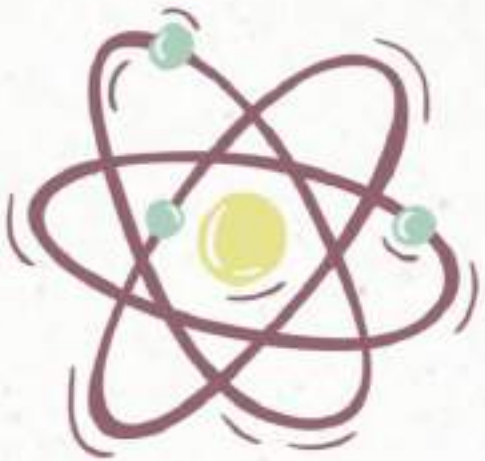
Pediatric:

0.05-0.3 mg/kg/dose IV q5-10 min.



Medico-Legal Aspect

- Patients exposed to organophosphate (OP) should be observed for at least 12 hours in a high acuity setting; toxicity after this is unlikely
- Because of the risk of respiratory depression or recurrent symptoms after resolution of an acute cholinergic crisis, hospitalizing all symptomatic patients for at least 48 hours following resolution of symptoms is recommended
- The symptoms of OP poisoning can mimic other toxicities and disease processes. The clinician must keep in mind that misdiagnosis is a potential medicolegal pitfall





THANK YOU!