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An Overview on Cholinesterase Inhibitor Pesticides

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Abstract:

Cholinesterase inhibitor pesticides are a class of chemical agents primarily used in agriculture and public health for pest control. These compounds work by inhibiting the activity of cholinesterase enzymes, mainly acetylcholinesterase (AChE), which are essential for the normal functioning of the nervous system. The most common types include organophosphates and carbamates. Under normal conditions, AChE breaks down the neurotransmitter acetylcholine in synaptic clefts, thereby terminating nerve impulses. Cholinesterase inhibitors disrupt this process, causing accumulation of acetylcholine, which leads to continuous nerve stimulation, resulting in symptoms such as muscle twitching, respiratory distress, convulsions, and potentially death in severe cases. Due to their potent neurotoxicity, these pesticides pose significant health risks to humans, particularly to agricultural workers, children, and people living in areas of high pesticide use. Acute exposure can cause cholinergic syndrome, while chronic exposure has been linked to neurological disorders, cognitive impairment, and developmental effects. Moreover, environmental concerns arise due to their toxicity to non-target organisms, including beneficial insects, birds, and aquatic life. Efforts to regulate and monitor the use of cholinesterase inhibitors have increased globally, with some compounds banned or restricted in many countries. However, their use remains widespread in low- and middle-income countries due to their effectiveness and low cost.

Keywords: Cholinesterase Inhibitor Pesticides, organophosphorus, poisoning.

Introduction:

Pesticides are classified into herbicides, insecticides, fungicides and fumigants **(1)**. Among the insecticides, organophosphorus (OP) and carbamate compounds are accounted for human poisoning **(2)**.

These compounds act by inhibiting acetylcholinesterase enzyme, causing overstimulation of acetylcholine receptors (**3)**.

There are at least 13 types of OP compounds **(4)**. Carbamates are N-methyl carbamates derived from a carbamic acid **(5)**. The three main classes of carbamate pesticides are known: carbamate insecticides, where R1 is a methyl group; carbamate herbicides, where R1 is an aromatic moiety; and carbamate fungicides, where R1 is a benzimidazole moiety **(6)**. R2 is an aromatic or aliphatic moiety, while R1 can be a methyl group, an aromatic moiety or a benzimidazole moiety.

Toxicokinetics of OP and carbamate:

Organophosphorus compounds:

(1) ***Absorption****:* OP pesticides are absorbed by almost all routes, including inhalation, ingestion, and dermal absorption **(7)**.

The degree of absorption is affected by many factors, including the following **(8) :**

- The lipophilicity of the agent involved (the more lipophilic, the more absorption occurs).
- The existence of solvents (e.g., xylene) and emulsifiers mixed with pesticides in the formulation increases absorption.
- Pesticide volatility (e.g., dichlorvos is much more volatile than malathion).
- Form of preparation (powders, especially the fine powder is more completely absorbed than others).

(2) ***Distribution and Storage:*** OP pesticides are prone to accumulate promptly in the fat, liver, kidneys, and salivary glands due to their lipophilicity. The phosphorothioates (P=S) are more lipophilic than phosphates (P=O). For example, diazinon, parathion, and bromophos are more lipophilic than dichlorvos Hence, these are stored broadly in fat, and it may also account for the prolonged intoxication and clinical deterioration even after apparent recovery from the poisoning from these OP insecticides **(9)**. This variable lipophilicity also explains why compounds vary in the ease with which they cross the blood-brain barrier **(10)**.

(3) **Biotransformation*:*** OP pesticides can have a direct inhibitory effect on the acetylcholinesterase enzyme (AChE) without necessitating initial metabolism after absorption. These direct-acting compounds are called oxons and differ from other compounds known as thions, which require metabolic activation within the body to become active. Thion organophosphorus compounds are activated by cytochrome P450 (CYP450) enzymes, primarily located in the liver and intestine **(11)**.

(4) ***Elimination:*** Most metabolites are eliminated in urine and lesser amounts in faeces. Some OP compounds with less lipophilicity can be eliminated in hours (dichlorvos), whereas the oxon of chlorpyrifos or demeton-S-methyl might continue for several days since they are widely stored in fat (**12)**.

Carbamate:

Carbamates are absorbed from the skin, lungs, conjunctiva, mucous membranes and gastrointestinal tract (GIT). Dermal absorption appears to be low, with increasing absorption in cases of disruption in the skin and exposure to highly toxic carbamates. Rat data shows peak inhibition of cholinesterases by 30 minutes after oral administration. After massive exposures, patients may become symptomatic within 5 minutes. The time to symptom onset is dependent on the exposure dose and the toxicity of the given carbamate. Highly lipophilic carbamates will redistribute into fat stores from the extracellular fluid quickly and have decreased clinical effects initially **(5)**.

Carbamates are hepatically metabolized via hydrolysis, hydroxylation, and conjugation, and 90% are renally excreted in a matter of days. Data are conflicting on the central nervous system (CNS) and cerebrospinal fluid penetration of carbamates. Adults tend to have less CNS toxicity, whereas, in paediatric exposures, CNS depression is often a predominant symptom. Importantly, carbamates do not undergo the "ageing" that occurs during the phosphorylation of OP pesticides to acetylcholinesterase**,** and the carbamate-cholinesterase bond hydrolyses spontaneously within hours **(13)**.

Toxicodynamics of OP and carbamate:

OP and carbamate pesticides both inhibit the synaptic acetylcholinesterase enzyme (AChE). Synaptic AChE normally prevents further downstream neurotransmission by hydrolyzing acetylcholine to acetic acid and choline **(14) (Figure 1)**.

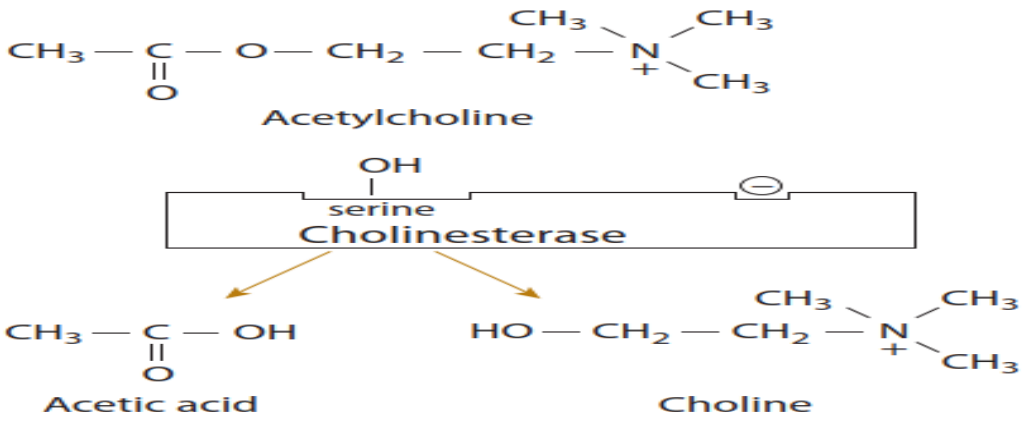

Figure (1): Normal metabolism of acetylcholine by acetylcholinesterase to choline and acetic acid. (**15**)

Acetic acid feeds into the Krebs cycle, whereas choline is taken back up by the neuron and resynthesized into new acetylcholine. Subsequently, acetylcholine accumulates in the nerve or myoneuronal synapse, which leads to characteristic toxic manifestations (cholinergic toxidrome). True AChE is found not only in nervous tissue, but also on the surface of erythrocytes (erythrocyte or red blood cell cholinesterase). Butyryl cholinesterase (also known as pseudocholinesterase or plasma cholinesterase) is found primarily in the liver and is responsible for xenobiotic metabolism (e.g., cocaine and succinylcholine) (**16**). It is important to note that erythrocyte AChE activity more closely mirrors neuronal AChE activity than does butyryl cholinesterase and is a better marker for neuronal physiologic status **(17)**.

<u>Toxicodynamic Differences Between Organophosphorus and Carbamates:</u>

The unique pharmacodynamics of organophosphorus and carbamates and their differences in interaction with AChE play a role in the clinical toxicity differences, as well as implications for antidotal therapy. Within the anticholinesterase protein catalytic site lays a serine hydroxyl group (–OH); The serine group becomes phosphorylated once the leaving group (X) is released. At this point, the OP–serine bond can spontaneously hydrolyze and the enzyme regains its function or an R group leaves (ages), it becomes irreversibly phosphorylated, and the enzyme is permanently inhibited **(Figure 2)** (**16**).

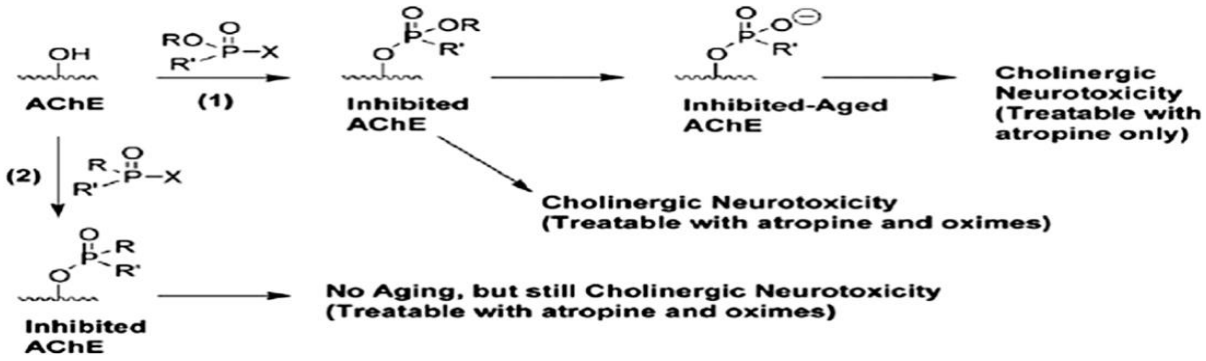

Figure (2): Toxicodynamics of OP pesticides: Phosphonyl (1) and phosphinyl (2) organophosphorus molecules bind to the acetyl-cholinesterase enzyme with resultant loss of the leaving group (X). The acetylcholinesterase (AChE) enzyme is now inhibited in both cases and cholinergic toxicity ensues. Before the loss of the R group in (1), both complexes are treatable with atropine and oximes. However, after the loss of the R group (1), the OP has "aged" and the AChE enzyme is irreversibly inhibited (**16**).

Carbamates also inhibit AChE enzyme in an identical fashion; however, the carbamate–AChE bond is weaker than that formed by OP. Thus, carbamate–AChE bonds spontaneously hydrolyse more rapidly and AChE function returns typically within 24 to 48 hours. In contrast with OP, carbamates cannot age and prolonged toxicity is uncommon (**16**).

Pathophysiology:

The 2 acetylcholine receptor subtypes found in humans and animals are the muscarinic and nicotinic receptors. These receptors are further subclassified according to their locations in the body and what occurs after acetylcholine binds to the receptor. In general, muscarinic receptors are found in the central nervous system (CNS), exocrine glands, and the hollow end-organs innervated by the parasympathetic system, while nicotinic receptors are located in the postganglionic neurons of both the parasympathetic and sympathetic chains, the adrenal medulla, and the neuromuscular junction (Figure 3). Both are found in the brain **(18)**.

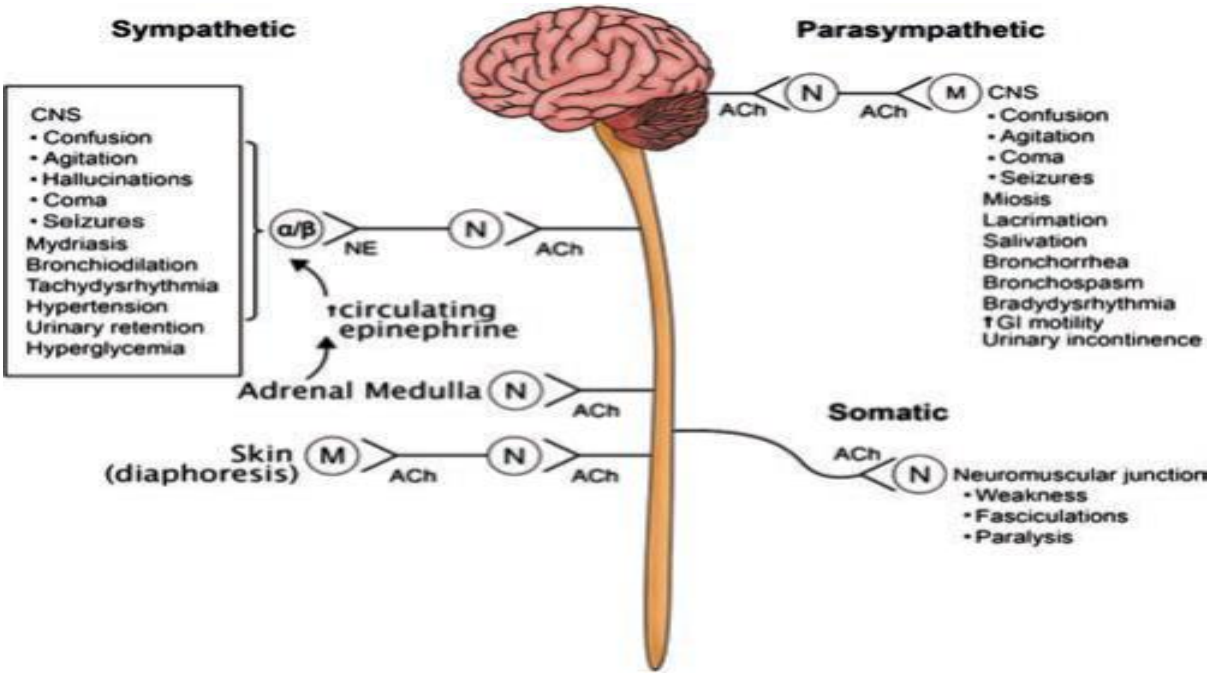

Figure (3): Pathophysiology of cholinergic syndrome as it affects the autonomic and somatic nervous systems (**15**).

Excess acetylcholine at the 2 receptor subtypes results in different end-organ effects. When poisoning by OP and carbamate xenobiotics occurs, toxicity varies and may manifest with primarily nicotinic effects, muscarinic effects or a combination of the two. Acetylcholine excess at the neuromuscular junction results in paralysis. Additionally, cholinergic neurons interact with other neurotransmitter systems ultimately leading to gamma-aminobutyric acid (GABA) inhibition and *N*-methyl-D-aspartate activation, which may in part be responsible for CNS-mediated respiratory depression and seizure activity **(19)**.

Routes of exposure to organophosphorus and carbamate pesticides: (20)

- OP and carbamates are absorbed through all routes.
- Ingestion and inhalation lead to the immediate onset of symptoms if vaporised or misted.
- Dermal exposure may have immediate local effects (local diaphoresis and fasciculations) and delayed systemic effects.

Clinical picture of organophosphorus and carbamate poisoning:

Acute toxicity:

Cholinergic excess:

The clinical manifestations of poisoning are mainly due to muscarinic, nicotinic and central nervous system (CNS) receptors overstimulation **(21)**.

The muscarinic signs can be remembered by use of one of two mnemonics: **(22)**

- **SLUDGE/BBB**: **S**alivation, **L**acrimation, **U**rination, **D**efecation, **G**astric **E**mesis, **B**ronchorrhea, **B**ronchospasm, **B**radycardia
- **DUMBELS**:**D**efecation, **U**rination, **M**iosis, **B**ronchorrhea/**B**ronchospasm/**B**radycardia, **E**mesis, **L**acrimation, **S**alivation.

The nicotinic signs of AChE inhibitor toxicity can be remembered by the following days of the week **(23):**

- Monday = Mydriasis
- Tuesday = Tachycardia
- Wednesday = Weakness
- Thursday = Hypertension
- Friday = Fasciculations

Nicotinic and muscarinic receptors also have been identified in the brain and may contribute to central respiratory depression, lethargy, seizures, and coma **(24)**.

Table (1): Signs and symptoms of acute poisoning with anticholinesterase compounds **(25)**.

Signs and Symptoms of Acute Poisoning with Anticholinesterase Compounds

SITE AND RECEPTOR AFFECTED	MANIFESTATIONS
Exocrine glands (M)	Increased salivation, lacrimation, perspiration
Eyes (M)	Miosis, blurred vision
Gastrointestinal tract (M)	Abdominal cramps, vomiting, diarrhea
Respiratory tract (M)	Increased bronchial secretion, bronchoconstriction
Bladder (M)	Urinary frequency, incontinence
Cardiovascular system (M)	Bradycardia, hypotension
Cardiovascular system (N)	Tachycardia, transient hypertension
Skeletal muscles (N)	Muscle fasciculations, twitching, cramps, generalized weakness, flaccid paralysis
Central nervous system (M, N)	Dizziness, lethargy, fatigue, headache, mental confusion, depression of respiratory centers, convulsions, coma

M, muscarinic receptors; N, nicotinic receptors.

Cardiac manifestations: (26)

Cardiac or hemodynamic abnormalities like hypotension, bradycardia, or tachycardia are typical in acute OP poisoning and result from various mechanisms, such as:

1. Autonomic disturbances (due to over stimulation of muscarinic and/or nicotinic acetylcholine receptors),
2. Consequences of hypovolemia or hypoxia, peripheral vasodilatation, and direct myocardial damage.

Muscarinic effects on the cardiovascular system include bradycardia, conduction block, and hypotension (parasympathetic overactivity), whereas nicotinic stimulation leads to hypertension and tachycardia (sympathetic overactivity).

The cardiac electrophysiological abnormalities usually include ventricular tachyarrhythmias, torsades de pointes and various electrocardiography (ECG) abnormalities such as QT interval prolongation, ST segment changes, tall T waves, premature contractions and atrioventricular block. These abnormalities are strongly confounded by the hypoxia and hypovolemia associated with cholinergic crisis and more commonly reported before atropinization.

Table (2): Cardiac manifestations of organophosphorus insecticide **(10).**

Bradycardia, tachycardia
Ventricular arrhythmias
Torsades de pointes
Ventricular fibrillation
Asystole
ECG changes
ST-segment changes
Peaked T waves
Atrioventricular block
QTc interval prolongation
Histopathological changes
Lysis of myofibrils
Z-band abnormalities

Respiratory manifestations:

Fatalities from acute organophosphorus agent poisoning generally result from respiratory failure due to a combination of depression of the CNS respiratory center, neuromuscular weakness, excessive respiratory secretions and bronchoconstriction. Fatalities also occur due to cardiovascular collapse; although the mechanism of this dysfunction is not completely understood, inappropriate vasodilation may play a role **(27)**.

Additional effects:

Several case reports describe acute kidney injury (AKI) requiring renal replacement therapy in the setting of severe organophosphate poisoning **(28, 29)**.

Acute pancreatitis may complicate poisoning caused by either organophosphates or carbamates **(30)**.

sequelae of acute toxicity:

1. Intermediate (neurologic) syndrome:

Ten to 40 per cent of patients poisoned with organophosphorus pesticides develop a distinct neurologic disorder 24 to 96 hours after exposure. This disorder referred to as the "intermediate syndrome", consists of characteristic

neurological findings including neck flexion weakness, decreased deep tendon reflexes, cranial nerve abnormalities, proximal muscle weakness and respiratory insufficiency **(31)**.

Risk factors for the development of intermediate syndrome appear to include exposure to a highly fat-soluble organophosphorus agent and may be related to inadequate doses of oximes **(32)**.

The intermediate syndrome has rarely been described following carbamate poisoning **(33)**.

2. Delayed and long-term neuropathology:

Organophosphorus agent-induced delayed neuropathy (OPIDN) can develop days to weeks after acute toxicity, and it is more frequently observed with specific compounds including chlorpyrifos, dichlorvos, isofenphos, and methamidophos **(34)**. This neuropathy arises due to the inhibition of the neuropathy target esterase enzyme, which catalyses the breakdown of the major phospholipid within cell membranes in nervous tissues. The symptoms associated with this condition include muscle cramping in the lower extremities, distal numbness and paresthesia affecting the extremities, which can advance to the loss of deep tendon reflexes **(23)**.

3. Neuropsychiatric deficits:

Individuals who survive acute organophosphorus agent poisoning may also experience neuropsychiatric deficits such as confusion, memory impairment, lethargy, psychosis, irritability and Parkinson-like symptoms **(23)**.

Chronic toxicity: Personnel who apply pesticides or who handle different formulations in closed environments are at risk, and the severity of risk depends upon: the duration of handling or application, patient genetics and chronic diseases **(35)**.

Several studies have confirmed the link between exposure to pesticides and the incidence of a large number of adverse outcomes, such as reproductive effects, endocrine disorders, birth defects, and neurological, hepatic, respiratory, hematopoietic, and immunological effects, as well as the development of various types of cancer, including multiple myeloma, leukaemia, and non-Hodgkin's lymphoma **(36)**. In addition, the incidence of diabetes, obesity and cardiovascular diseases has also been associated with pesticide exposure **(37)**.

Management of organophosphorus and carbamate poisoning:

Diagnosis: The diagnosis of OP or carbamate poisoning is typically a clinical diagnosis based on history and physical examination. The simultaneous presence of both muscarinic and nicotinic effects should strongly suggest OP exposure, and empiric immediate treatment is warranted. Similarly, any multi-causality incident where multiple victims have seizures, become comatose, or suffer cardiac arrest should raise suspicion for nerve agent release.

Exposure is typically confirmed in 1 of 2 ways:

The first method involves the detection of organophosphorus metabolites (para-nitrophenol or dialkyl phosphate) in the urine mostly useful in chronic exposure.

The second approach involves the assay of AChE enzyme level and is most useful when the diagnosis is not evident. Cholinesterase activity levels are often not readily available within a practical time window for emergency clinicians **(38)**. However, laboratory testing can provide useful parameters to follow while managing an intoxicated patient and can give insight into the disease course and response to therapy **(39)**. In general, erythrocyte cholinesterase activity correlates best with neuronal AChE activity at the neuromuscular junction and is the preferred test to evaluate oxime effectiveness **(40)**.

Plasma cholinesterase activity can also be useful, but there are a number of mitigating factors and differences with plasma cholinesterase assays that affect their utility **(39)**.

While in acute carbamate toxicity, measurement of cholinesterase activity is unlikely to be helpful clinically because of the rapid course of the intoxication.

Laboratory assay should take less than 3 min and employ minimal dilution, and samples must be kept on ice or frozen at -20°C during transportation **(10)**.

Treatment of organophosphorus and carbamate poisoning:

Stabilization:

Most patients who succumb to OP or carbamate exposure die from loss of airway and respiratory drive (**41)**.

Airway protection consists of suction of copious oropharyngeal secretions and vomit, if present. Endotracheal intubation and mechanical ventilation are often needed. It is important to increase tissue oxygenation as much as possible prior to administration of atropine in order to minimize the risk of ventricular fibrillation **(8)**.

The use of succinylcholine for rapid sequence intubation is discouraged as there will be prolonged paralysis because succinylcholine is metabolized by plasma cholinesterases (**42)**.

Decontamination:

Removal from the source and patient decontamination is often performed before health care facility arrival and ideally should be performed by health care providers in appropriate personal protective equipment **(43)**.

Further decontamination should be addressed only after initial stabilization and injury assessment by removal of all clothing and equipment **(44)** then the patient should be washed down with soap and water (**45)**.

Forced emesis is contraindicated because of the risk of aspiration and seizures, some clinicians may elect to do gastric lavage in patients who present less than one hour following ingestion of an organophosphorus agent.

Activated charcoal (AC) should be given to patients presenting within one hour of an organophosphorus agent or carbamate ingestion. The standard dose is 1 g/kg (maximum dose 50 g) **(33)**.

Pharmacological treatment options:

The pharmacologic section is divided into 3 main sections based on their therapeutic mechanisms: Antimuscarinic agents, oxime therapy, and seizure control with benzodiazepines.

Antimuscarinics:

1) Atropine

Atropine sulfate should be administered intravenous (IV). Atropine works as a physiological antidote in anticholinesterase toxicity by competitively blocking the action of acetylcholine at muscarinic receptors, treating the excessive parasympathetic stimulation induced by AChE inactivation **(46)**.

Atropine is a competitive inhibitor of muscarinic receptors both in the CNS and peripheral nervous systems **(47)**. Rapid administration of atropine in rapidly escalating doses is recommended. The patient should receive 1 to 2 mg of atropine initially, and the dose should be doubled every 5 minutes until pulmonary secretions are dried, and the patient has an adequate heart rate and blood pressure **(48)**. Once control is achieved with bolus dosing, an atropine infusion should be initiated at 10% to 20% of the total dose required to stabilize the patient per hour **(49)**.

2) Glycopyrrolate

Because atropine is able to cross the blood-brain barrier, CNS anticholinergic toxicity may occur before adequate control of peripheral cholinergic symptoms. Atropine treatment can be replaced with glycopyrrolate, a peripheral

antimuscarinic agent without CNS muscarinic receptor activity. Despite limited evidence, glycopyrrolate is not inferior to atropine and should be considered an appropriate alternative to atropine if atropine supply is limited **(50)**.

Finally, if bronchorrhea and bronchoconstriction are the primary forms of toxicity, Ipratropium can be administered by inhalation with direct effects on the target end organ **(51)**.

Oxime Therapy:

Therapeutic oximes (like pralidoxime, obidoxime) work as reactivators of inhibited AChE, but they are efficient only as long as some of the inhibited enzyme still remains in the unaged form. Such compounds may be highly effective in restoring some active AChE and normal respiratory function of the diaphragm, where the nicotinic effects of excessive acetylcholine (ACh) are not antagonized by atropine **(52)**.

Furthermore, in the continued presence of poison in the blood, there will be an ongoing struggle between reactivation and re-inhibition of AChE. In these conditions, in spite of there may be no significant medical benefit following the establishment of oxime therapy, this should never prevent continuous intervention with oxime therapy **(53)**.

Administration of oximes to carbamate-poisoned patients is likewise controversial. However, the preponderance of the data suggests that oxime therapy in the setting of carbamate toxicity improves morbidity and mortality (**54)**.

Seizure control with benzodiazepines:

Uncontrolled seizures and convulsions may lead to brain damage **(55).** Seizures are common among hypoxia conditions caused by OP pesticides poisoning **(56)**.

1) Diazepam: is considered the first line of treatment for OP-induced seizures **(57).** The required dose of diazepam is 10–20 mg through an IV route in adults and 300–400μg/kg IV in children. The dosage can be repeated as per the requirement **(58)**.

2) Lorazepam: is another benzodiazepine that has a greater advantage over IV diazepam. It can terminate elevated seizure rates and prevent convulsions for a prolonged period. In the OP-induced seizure condition, 4 mg/dose of lorazepam can be given by slow IV at 2 mg/min, and if it persists after 5–10 min, then 4 mg can be administered again **(59)**.

3) Midazolam: is also used as intravenous (IV) or intramuscular (IM) shots for managing OP-induced seizures. However, the administration of midazolam should be immediate, and delaying may cause poor potency. The recommended dose of midazolam is 2.2 mg/kg, and it also varies depending on the type of OP and how quickly it has been administered with the appearance of first symptoms of a seizure **(60)**.

Sodium bicarbonate:

Blood alkalinization using sodium bicarbonate has been prescribed for many years. The exact mechanism of action is uncertain but may involve enhanced OP clearance via pH-mediated hydrolysis, direct effect on neuromuscular activity or improved efficacy of oximes **(61)**.

Magnesium sulfate:

Magnesium decreases the release of synaptic acetylcholine by blocking calcium channels. Animal studies have suggested an advantage in minimizing cholinergic activation after OP poisoning. Magnesium may also reduce the risk of ventricular tachycardia in patients with tachycardia due to nicotinic stimulation **(62)**.

Lipid emulsions:

In recent years, lipid emulsion has been used for the treatment of OP pesticides toxicity because some OP pesticides are extremely lipid-soluble and are formulated in lipid-soluble solvents **(53)**.

The treatment algorithm for OP and carbamate insecticide poisoning is summarized in **(Figure 4)**.

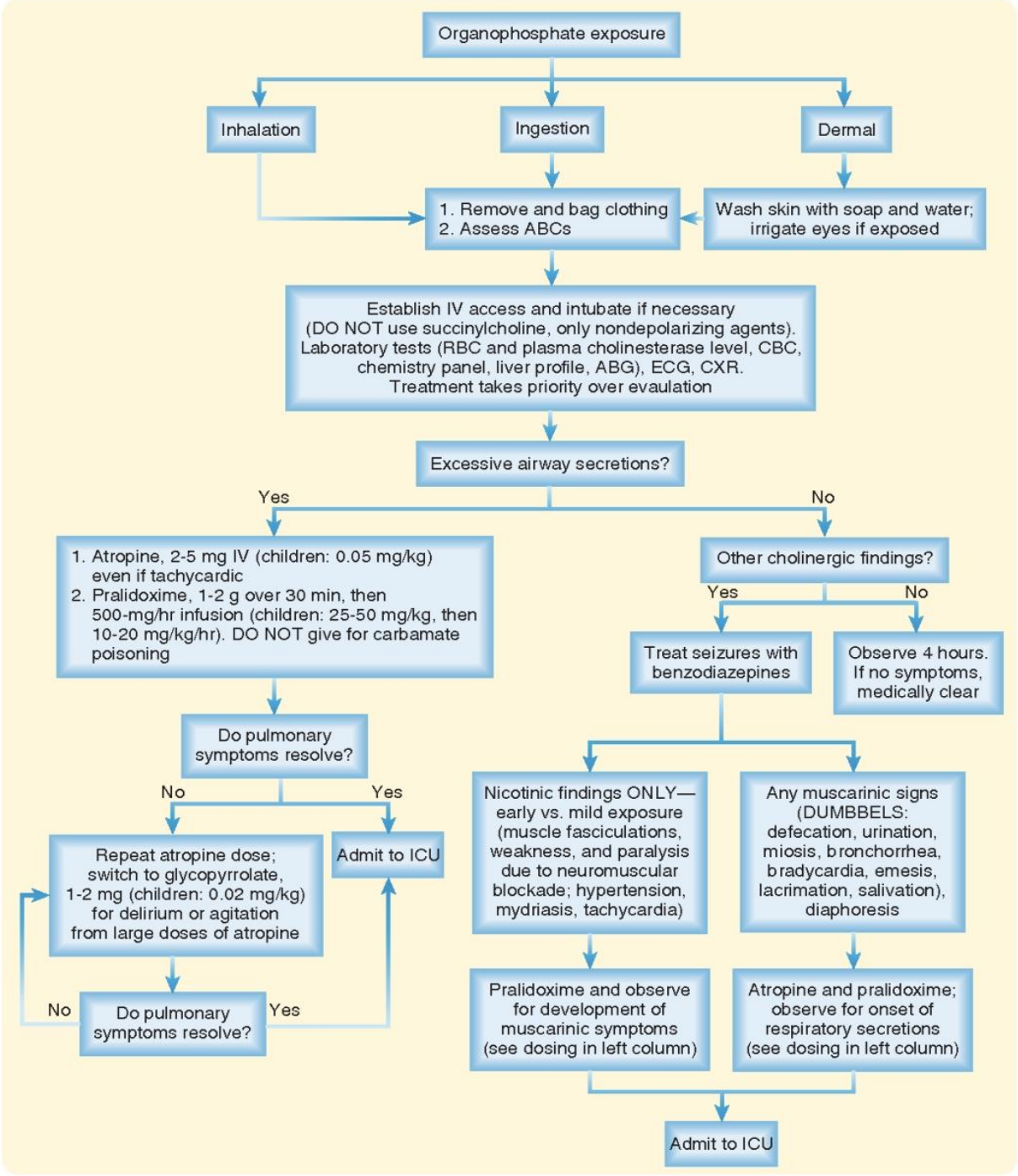

Figure (4): Treatment algorithm for organophosphorus insecticide poisoning **(63)**.

ABC: Airway, breathing, and circulation, ABG: arterial blood gas, CBC: complete blood count, CXR: chest radiograph, ECG: electrocardiography, ICU: intensive care unit, IV: intravenous, RBC: red blood cell.

References:

1. Georgiadis M, Tsarouhas K, Tsitsimpikou C, Vardavas A, Rezaee R, Tsatsakis AM (2018). Pesticide exposure and health effects: Towards a molecular epidemiological approach. Toxicol Lett. 295:140–49.
2. Page, A., Liu, S., Gunnell, D., Astell-Burt, T., Feng, X., Wang, L., & Zhou, M. (2017). Suicide by pesticide poisoning remains a priority for suicide prevention in China: analysis of national mortality trends 2006–2013. Journal of affective disorders, 208, 418-423.
3. Dungdung, A., Kumar, A., Kumar, B., Preetam, M., Tara, R. K., & Saba, M. K. (2020). Correlation and prognostic significance of serum amylase, serum lipase, and plasma cholinesterase in acute organophosphorus poisoning. Journal of family medicine and primary care, 9(4), 1873-1877.
4. Gupta, R. C. (2006). Classification and uses of organophosphates and carbamates. In Toxicology of organophosphate & carbamate compounds (pp. 5-24). Academic Press.
5. Silberman, J., & Taylor, A. (2024). Carbamate Toxicity. StatPearls [Internet].
6. Sousa, S., Maia, M. L., Correira-Sá, L., Fernandes, V. C., Delerue-Matos, C., Calhau, C., & Domingues, V. F. (2020). Chemistry and toxicology behind insecticides and herbicides. Controlled release of pesticides for sustainable agriculture, 59-109.
7. Kwong, T. C. (2002). Organophosphate pesticides: biochemistry and clinical toxicology. Therapeutic drug monitoring, 24(1), 144-149.
8. Kazemi, M., Tahmasbi, A. M., Valizadeh, R., Naserian, A. A., & Soni, A. (2012). Organophosphate pesticides: A general review. Agricultural science research journals, 2.
9. García-Rojo, G., Gámiz, F., Ampuero, E., Rojas-Espina, D., Sandoval, R., Rozas, C., ... & Pancetti, F. (2017). In vivo sub-chronic treatment with dichlorvos in young rats promotes synaptic plasticity and learning by a mechanism that involves acylpeptide hydrolase instead of acetylcholinesterase inhibition. Correlation with endogenous β-amyloid levels. Frontiers in Pharmacology, 8, 483.
10. Vale, J.A., Bradberry, S.M. (2017). Organophosphate and Carbamate Insecticide. In: Brent, J., et al. Critical Care Toxicology. Springer, Cham.
11. Buratti, F. M., Volpe, M. T., Meneguz, A., Vittozzi, L., & Testai, E. (2003). CYP-specific bioactivation of four organophosphorothioate pesticides by human liver microsomes. Toxicology and Applied Pharmacology, 186(3), 143-154.
12. Sidhu, G. K., Singh, S., Kumar, V., Dhanjal, D. S., Datta, S., & Singh, J. (2019). Toxicity, monitoring and biodegradation of organophosphate pesticides: a review. Critical reviews in environmental science and technology, 49(13), 1135-1187.
13. Lee, D. H., Jung, K. Y., Choi, Y. H., & Cheon, Y. J. (2014). Body mass index as a prognostic factor in organophosphate-poisoned patients. The American journal of emergency medicine, 32(7), 693-696.
14. McHardy, S. F., Wang, H. Y. L., McCowen, S. V., & Valdez, M. C. (2017). Recent advances in acetylcholinesterase Inhibitors and Reactivators: an update on the patent literature (2012-2015). Expert opinion on therapeutic patents, 27(4), 455-476.
15. Nelson, L. S., & Goldfrank, L. R. (2019). Goldfrank's toxicologic emergencies. (No Title).
16. King, A. M., & Aaron, C. K. (2015). Organophosphate and carbamate poisoning. Emergency Medicine Clinics, 33(1), 133-151.
17. Lionetto, M. G., Caricato, R., Calisi, A., Giordano, M. E., & Schettino, T. (2013). Acetylcholinesterase as a biomarker in environmental and occupational medicine: new insights and future perspectives. BioMed research international, 2013(1), 321213.
18. Vanderah, T. W. (Ed.). (2024). Katzung's basic & clinical pharmacology. New York: McGraw Hill.
19. Kozhemyakin, M., Rajasekaran, K., & Kapur, J. (2010). Central cholinesterase inhibition enhances glutamatergic synaptic transmission. Journal of neurophysiology, 103(4), 1748-1757.
20. Amir, A., Raza, A., Qureshi, T., Mahesar, G. B., Jafferi, S., Haleem, F., ... & Khan, M. A. (2020).

Organophosphate poisoning: demographics, severity scores and outcomes from National Poisoning Control Centre, Karachi. Cureus, 12(5).

21. Hammad, S. A. E., Allam, H. A. F., & El-Farouny, R. H. (2024). Study of Acute Anticholinesterase Poisoning Cases and the Predictive Relevance of Caspase Markers. Menoufia Medical Journal, 37(2), Page1-Page.
22. Adeyinka, A., & Kondamudi, N. P. (2024). Cholinergic Crisis. StatPearls [Internet].
23. Robb, E. L., Regina, A. C., & Baker, M. B. (2024). Organophosphate toxicity.[updated 2023 Nov 12]. StatPearls. Treasure Island (FL): StatPearls Publishing.
24. Pakala, R. S., Brown, K. N., & Preuss, C. V. (2023). Cholinergic Medications. In StatPearls. StatPearls Publishing.
25. Costa, C., Miozzi, E., Teodoro, M., & Fenga, C. (2019). Influence of genetic polymorphism on pesticide-induced oxidative stress. Current Opinion in Toxicology, 13, 1-7.
26. Pannu, A. K., Bhalla, A., Vishnu, R. I., Garg, S., Dhibar, D. P., Sharma, N., & Vijayvergiya, R. (2021). Cardiac injury in organophosphate poisoning after acute ingestion. Toxicology Research, 10(3), 446-452.
27. Asari, Y., Kamijyo, Y., & Soma, K. (2004). Changes in the hemodynamic state of patients with acute lethal organophosphate poisoning. Veterinary and human toxicology, 46(1), 5-9.
28. Agostini, M., & Bianchin, A. (2003). Acute renal failure from organophospate poisoning: a case of success with haemofiltration. Human & experimental toxicology, 22(3), 165-167.
29. Cavari, Y., Landau, D., Sofer, S., Leibson, T., & Lazar, I. (2013). Organophosphate poisoning-induced acute renal failure. Pediatric emergency care, 29(5), 646-647.
30. Sahin, I. Ç., Onbasi, K., Sahin, H., Karakaya, C. E. N. G. İ. Z., Ustun, Y. U. S. U. F., & Noyan, T. E. V. F. İ. K. (2002). The prevalence of pancreatitis in organophosphate poisonings. Human & experimental toxicology, 21(4), 175-177.
31. Indira, M., Andrews, M. A., & Rakesh, T. P. (2013). Incidence, predictors, and outcome of intermediate syndrome in cholinergic insecticide poisoning: a prospective observational cohort study. Clinical toxicology, 51(9), 838-845.
32. Groszek, B., Pach, J., & Kłys, M. (1995). Intermediate syndrome in acute fenitrothion poisoning. Przeglad lekarski, 52(5), 271-274.
33. Bird, S. (2024). Organophosphate and Carbamate poisoning. UpToDate. updated September 20, 2024
34. Lotti, M., & Moretto, A. (2005). Organophosphate-induced delayed polyneuropathy. Toxicological reviews, 24(1), 37-49.
35. Benitez-Trinidad, A. B., Medina-Díaz, I. M., Bernal-Hernández, Y. Y., Barrón-Vivanco, B. S., González-Arias, C. A., Herrera-Moreno, J. F., ... & Rojas-García, A. E. (2018). Relationship between LINE-1 methylation pattern and pesticide exposure in urban sprayers. Food and chemical toxicology, 113, 125-133.
36. Mu, Y., Hu, B., Gao, N., & Pang, L. (2021). Prognostic value of the neutrophil-to-lymphocyte ratio in acute organophosphorus pesticide poisoning. Open life sciences, 16(1), 703-710.
37. Legler, J., Hamers, T., van der Sluijs, M. V. E., Schoeters, G., van der Ven, L., Eggesbo, M., ... & Trnovec, T. (2011). The OBELIX project: early life exposure to endocrine disruptors and obesity. The American journal of clinical nutrition, 94, S1933-S1938.
38. Rajapakse, B. N., Thiermann, H., Eyer, P., Worek, F., Bowe, S. J., Dawson, A. H., & Buckley, N. A. (2011). Evaluation of the Test-mate ChE (cholinesterase) field kit in acute organophosphorus poisoning. Annals of emergency medicine, 58(6), 559-564.
39. Davies, J. O., Eddleston, M., & Buckley, N. A. (2008). Predicting outcome in acute organophosphorus poisoning with a poison severity score or the Glasgow coma scale. QJM: An International Journal of Medicine, 101(5), 371-379.
40. Thiermann, H., Szinicz, L., Eyer, P., Zilker, T., & Worek, F. (2005). Correlation between red blood cell acetylcholinesterase activity and neuromuscular transmission in organophosphate poisoning. Chemico-

biological interactions, 157, 345-347.

41. Konickx, L. A., Bingham, K., & Eddleston, M. (2014). Is oxygen required before atropine administration in organophosphorus or carbamate pesticide poisoning?–A cohort study. Clinical Toxicology, 52(5), 531-537.
42. Sener, E. B., Ustun, E., Kocamanoglu, S., & Tur2, A. (2002). Prolonged apnea following succinylcholine administration in undiagnosed acute organophosphate poisoning. Acta anaesthesiologica scandinavica, 46(8), 1046-1048.
43. Macintyre, A. G., Christopher, G. W., Eitzen Jr, E., Gum, R., Weir, S., DeAtley, C., ... & Barbera, J. A. (2000). Weapons of mass destruction events with contaminated casualties: effective planning for health care facilities. Jama, 283(2), 242-249.
44. Kales, S. N., & Christiani, D. C. (2004). Acute chemical emergencies. New England Journal of Medicine, 350(8), 800-808.
45. Koenig, K. L., Boatright, C. J., Hancock, J. A., Denny, F. J., Teeter, D. S., Kahn, C. A., & Schultz, C. H. (2008). Health care facility-based decontamination of victims exposed to chemical, biological, and radiological materials. The American journal of emergency medicine, 26(1), 71-80.
46. Sunger S, Guven M (2001). Antidotal efficacy of atropine and obidoxime in acute organophosphate poisoning. J Appl Toxicol. 21(1):55–58.
47. Shih, T. M., Rowland, T. C., & McDonough, J. H. (2007). Anticonvulsants for nerve agent-induced seizures: the influence of the therapeutic dose of atropine. The Journal of pharmacology and experimental therapeutics, 320(1), 154-161.
48. Eddleston, M., Buckley, N. A., Checketts, H., Senarathna, L., Mohamed, F., Sheriff, M. R., & Dawson, A. (2004). Speed of initial atropinisation in significant organophosphorus pesticide poisoning—a systematic comparison of recommended regimens. Journal of Toxicology: Clinical Toxicology, 42(6), 865-875.
49. Eddleston, M., Buckley, N. A., Eyer, P., & Dawson, A. H. (2008). Management of acute organophosphorus pesticide poisoning. The Lancet, 371(9612), 597-607.
50. Choi, P. T., Quinonez, L. G., Cook, D. J., Baxter, F., & Whitehead, L. (1998). The use of glycopyrrolate in a case of intermediate syndrome following acute organophosphate poisoning. Canadian journal of anaesthesia, 45, 337-340.
51. Perrone, J., Henretig, F., Sims, M., Beers, M., & Grippi, M. A. (2003). A role for ipratropium in chemical terrorism preparedness. Academic Emergency Medicine, 10(3), 290-290.
52. Johnson, M. K., Jacobsen, D., Meredith, T. J., Eyer, P., Heath, A. J., Ligtenstein, D. A., ... & Haines, J. A. (2000). Evaluation of antidotes for poisoning by organophosphorus pesticides. Emergency Medicine, 12(1), 22-37.
53. Eddleston, M., & Chowdhury, F. R. (2016). Pharmacological treatment of organophosphorus insecticide poisoning: the old and the (possible) new. British journal of clinical pharmacology, 81(3), 462-470.
54. Rosman, Y., Makarovsky, I., Bentur, Y., Shrot, S., Dushnistky, T., & Krivoy, A. (2009). Carbamate poisoning: treatment recommendations in the setting of a mass casualties event. The American journal of emergency medicine, 27(9), 1117–1124.
55. Dingledine, R., Varvel, N. H., & Dudek, F. E. (2014). When and how do seizures kill neurons, and is cell death relevant to epileptogenesis?. Advances in experimental medicine and biology, 813, 109–122.
56. Eddleston, M., Eyer, P., Worek, F., Mohamed, F., Senarathna, L., Von Meyer, L., ... & Buckley, N. A. (2005). Differences between organophosphorus insecticides in human self-poisoning: a prospective cohort study. The Lancet, 366(9495), 1452-1459.
57. Supasai, S., González, E. A., Rowland, D. J., Hobson, B., Bruun, D. A., Guignet, M. A., Soares, S., Singh, V., Wulff, H., Saito, N., Harvey, D. J., & Lein, P. J. (2020). Acute administration of diazepam or midazolam minimally alters long-term neuropathological effects in the rat brain following acute intoxication with diisopropylfluorophosphate. European journal of pharmacology, 886, 173538.
58. Bates, N. (2020). Poisons affecting the neurological system. The Veterinary Nurse, 11(3), 116-125.

59. Greenblatt, D. J., Shader, R. I., Franke, K., Maclaughlin, D. S., Harmatz, J. S., Allen, M. D., ... & Woo, E. (1979). Pharmacokinetics and bioavailability of intravenous, intramuscular, and oral lorazepam in humans. Journal of Pharmaceutical Sciences, 68(1), 57-63.
60. Reddy, S. D., & Reddy, D. S. (2015). Midazolam as an anticonvulsant antidote for organophosphate intoxication — a pharmacotherapeutic appraisal. Epilepsia, 56(6), 813-821.
61. Roberts, D. M., & Buckley, N. (2005). Alkalinisation for organophosphorus pesticide poisoning. Cochrane database of systematic reviews, (1).
62. Basher, A., Rahman, S. H., Ghose, A., Arif, S. M., Faiz, M. A., and Dawson, A. H. (2013): Phase II Study of Magnesium Sulfate in Acute Organophosphate Pesticide Poisoning. Clinical Toxicology, 51(1): 35-40.
63. Do, R.D., Ruha, A., Adams, J.G., Barton, E., Collins, J., & Deblieeux, P. (2008). Insecticides, Herbicides, and Rodenticides.