https://doi.org/10.48047/AFJBS.6.14.2024.5623-5645

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

An Overview on Management of Poisoning by Organophosphorus Compounds

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Article History

Volume 6, **Issue** 14, 2024

Received: 03 July 2024

Accepted: 17 August 2024

doi: 10.48047/AFJBS.6.14.2024.5623-5645

Abstract:

Background: Poisoning by Organophosphorus compounds (OPs) still is a major therapeutic problem. Intentional OPs insecticide poisoning results in up to 300.000 deaths each year and highly toxic OPs nerve agents pose a permanent threat for the civilian population and military forces. The therapeutic value of clinically used oximes, pralidoxime, obidoxime and TMB-4, in human OPs insecticide poisoning is under debate. Moreover, these oximes lack efficacy in poisoning by various nerve agents. An innumerable number of novel oximes have been synthesized in the past five decades to provide more effective oximes and compounds with improved blood–brain-barrier penetration. Novel compounds were tested with largely different experimental protocols in vitro and in animals in vivo. The lack of comparable experimental conditions and the absence of human in vivo studies hamper a well-founded evaluation of the available data.

Keywords: Poisoning, organophosphorus compounds, Toxicity.

1. Introduction

The Food and Agriculture Organization of the United Nations (FAO) defined the pesticides as “Any substance or mixture of substances or biological ingredients intended for repelling, destroying or controlling any pest or regulating plant growth”. Pesticides are classified according to the target organism into insecticides, rodenticides and herbicides ***(1).***

Most insecticides are synthetic and organic compounds that are classified into four major groups according to their chemical structures: (i) organochlorines such as dichlorodiphenyltrichloroethane (DDT); (ii) Organophosphorus compounds (OPs) such as malathion and temephos; (iii) carbamates and pyrethrins such as propoxur and carbaryl; and (iv) pyrethroids such as deltamethrin and lambda-cyhalothrin. Organophosphate insecticides are the most potentially harmful to vertebrates of these compounds ***(2).***

Regarding mechanism of action, there is a difference between these groups of insecticides. Organochlorines are a group of chlorinated compounds which are widely used. They are neurotoxic but the exact mechanism is not yet fully understood. The DDT-type insecticides alter the transport of sodium and potassium ions across axonal membranes, resulting in an increased negative after-potential and prolonged action potentials. As a result, repetitive firing and a spontaneous train of action potentials occur. They also induce hepatic degeneration and git irritation ***(3).***

OPs are esters of phosphoric acid. They induce phosphorylation of the acetylcholinesterase (AChE) at nerve endings. The inhibition may become irreversible after 36-48 hours (aging process). While carbamates are reversible AChE inhibitors by carbamylation of the enzyme and their duration of action is relatively short. Also, OPs can cross blood brain barrier while carbamates cant, so carbamates have no central effect ***(4).***

Pyrethroides are similar organic compounds isolated from the flowers of pyrethrums. They affect the sodium channels and lead to paralysis of the organism. Pyrethroides have a comparatively slight level of mammalian toxicity and have a fast biodegradation capacity. Exposure to very high levels of the compounds in air, food or water may cause giddiness, headache, vomiting, muscle twitching, low energy, convulsions and loss of consciousness ***(5).***

OPs started to appear from 50 years and then they spread throughout agriculture ***(6).***

In the early 1800s, the first Organophosphorus compound (OP) was synthesized through the reaction of alcohol with phosphoric acid. In 1854, tetraethyl pyrophosphate (TEPP), the first potent synthetic organophosphorus poison, was synthesized by Clermont. In 1872, OPs are considered as insecticides. In 1936, chemical warfare agents (tabun, sarin, soman) were produced by the German military. A decade later, England synthesized the fourth agent, VX ***(7).***

Because of the wide spread of different types of OPs and their easily accessibility as insecticides, there are a very large number of intoxications ranging between 750000 and 3000000 human intoxications world wide per year, resulting in hundreds of thousands of fatalities ***(8).***

According to The World Health Organization (WHO), more than 300 million cases of acute pesticide poisoning occur worldwide each year, with OP intoxication representing the majority of these cases ***(9).***

OPs contain esters of phosphoric acid in their structure. The most lethal forms of these compounds are known as nerve agents, which are used as chemical warfare agents ***(10).***

Organophosphorus poisoning is responsible for a large number of fatalities worldwide, particularly in developing countries ***(11).***

Because of insufficient enforcement of pesticide rules and insufficient financial resources, residual pesticide levels in Egyptian foods have been discovered to be greater than those discovered in developed countries ***(6).***

Chemical structure (Figure 1):

Organophosphates are chemical compounds formed by the esterification of phosphoric acid and alcohol ***(12).***

The general chemical structure of an OP consists of a central phosphorus atom with a double bond to oxygen or sulfur, where R1 and R2 are commonly alkyl or aryl groups connected to the phosphorus atom either through an oxygen or sulfur (phosphrothioates) or directly (phosphonates or phosphinates) ***(13).*** X is the most vulnerable to hydrolysis and so-called "leaving group," which is eliminated when the OP phosphorylates AChE ***(14).***

The presence of a P = S versus P = O bond is an essential factor for the human toxicity of organophosphorus insecticides ***(15).***

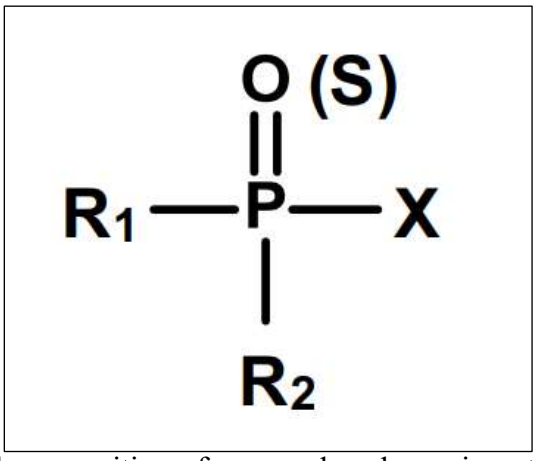


Figure 1. General chemical composition of organophosphorus insecticides with residues R1 and R2 and leaving group X ***(15).***

The R^1 and R^2 moieties are usually alkyl or aryl groups. When they are linked to phosphorus via oxygen, the resulting compound is called a phosphate , while bonding via sulfur results in a phosphorothiolate or S-substituted phosphorothioate ***(16).***

The most of organophosphorus insecticides presented under the class of phosphorothioate with thiophosphoryl bond (P = S) rather than a phosphoryl bond (P = O). Some OPs with P = O bonding are direct AChE inhibitors, while those with P = S bonding, which are phosphothioates, do not have anticholinesterase activities before biotransformation and thus are non-toxic per se. Apart from phosphates and phosphonates, most OPs only show anticholinesterase activities once they have undergone metabolic biotransformation ***(17).***

Classification of Organophosphorus compounds (Figure 2):

OPs are esters of phosphoric acid and/or thiophosphoric acid, classified based on their leaving (X) group as (i) aliphatic (e.g., malathion, dichlorvos, phorate, dimethoate, acephate, naled, dicrotophos and omethoate); (ii) phenyl (e.g., parathion, methyl-parathion, fenitrothion and tetrachlorvinphos); and (iii) heterocyclic (e.g., chlorpyrifos, diazinon, phosmet, azamethiphos and azinphos-methyl) derivatives ***(2).***

Aliphatic OPs have a carbon chain structure. Tetraethyl pyrophosphate was the first aliphatic OPs used in agriculture in 1946 ***(18).***

Phenyl OPs contain a phenyl ring with one of the ring hydrogen displaced by phosphorous and other hydrogens frequently displaced by chloride, nitrogen dioxide, methyle, cynide or sulfur. Parathion (ethyl parathion) was the first phenyl OPs used in agriculture in 1947. Rresidues of Phenyl OPs remain for long time as they are usually more stable than aliphatics ***(19).***

Heterocyclic OPs with O-P-S, N-P-S, and O-P-N functionalities showed anti-tumor, anti-inflammatory, and therapeutic activity ***(20).***

Figure 2. Chemical structure of:

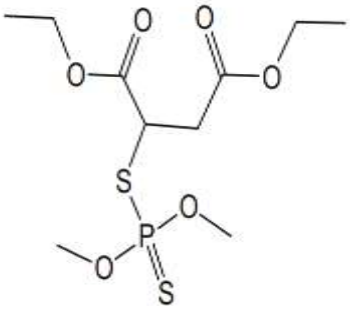


Figure 2a . malathion **(*17).***

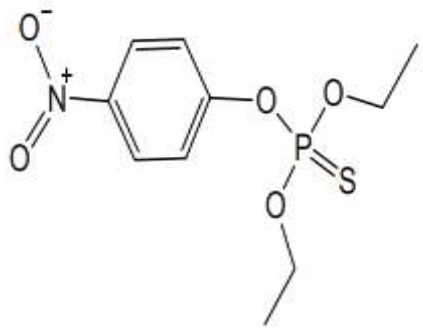


Figure 2b. parathion ***(17).***

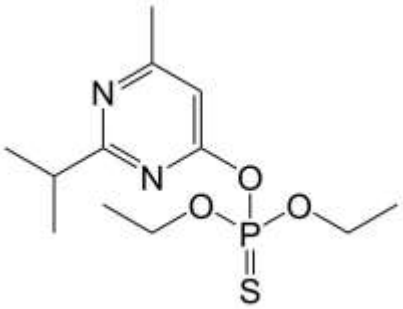


Figure 2c. diazinon ***(21).***

Routes of exposure to organophosphorus insecticides:

Because of easy accessibility of OPs in agriculture areas in addition to their sale over the counter, these areas contain the main bulk of poisoning cases ***(22).***

A. Occupational exposure:

Occupational exposure to insecticides usually occurs during the production, transportation, preparation and application of insecticides in the workplace. It is quite common among farmers. Occupational insecticides exposures occur during accidental spills of insecticides, leakages, incorrect uses of equipment, and non-compliance with safety guidelines. Respiratory inhalation and dermal absorption are considered as the primary routes of exposures to insecticides in occupational locations ***(23).***

B. Non occupational exposure:

OPs exposure may be intentional or unintentional. Suicidal exposure is more pronounced in rural area due to their ready availability and easy accessibility ***(24).***

Unintentional exposure especially occurs with children who live close to agricultural areas and those from agricultural families as they are exposed to higher levels of insecticides ***(25).***

Regarding that many farmers spray their agricultural fields with OPs in spring and summer months, suicidal and unintentional cases increase in these months ***(26).***

Approximately 3 million people worldwide are exposed to organophosphates, resulting in around 300,000 fatalities. In the United States, about 8000 cases of organophosphate exposure are reported, with very few fatalities. Since 2013, stricter government regulations have been applied for the sale of organophosphates ***(27).***

Pharmacokinetics of organophosphorus insecticides (Figure 3):

Absorption:

OPs cross lipid bilayers easily, such as alveolar and dermal membranes due to their lipophilicity, this make them efficiently absorbed by inhalation, ingestion and skin penetration ***(28).***

Inhalation is considered the most likely route of exposure to nerve agents. Solvent or additional additives in concentrates can boost absorption of OPs from the stomach and duodenum considering the nature of materials found in commercial preparations. Also, skin integrity, environmental temperature, skin hydration, and the solvent affect dermal absorption ***(29).***

Certain organochlorine insecticides, such as DDT, lindane, aldrin, and chlordane, are more lipid soluble than others, allowing them to be absorbed more easily via the skin. In contrast, pyrethroid insecticides are poorly absorbed though intact skin due to their low lipid solubility but can be well absorbed through inhalation and ingestion ***(23).***

The percentage of absorption of OPs by various routes varies significantly. For example, median lethal dose (LD50) of parathion for oral administration in rats is 3–8 mg/kg, which is quite toxic and essentially equivalent to dermal absorption at an LD50 dose of 8 mg/kg. On the other hand, the toxicity of some OPs (e.g., fosalone) at dermal route of administration is much lower than at oral route, with LD50 for rats being 1500 mg/kg and 120 mg/kg, respectively ***(30).***

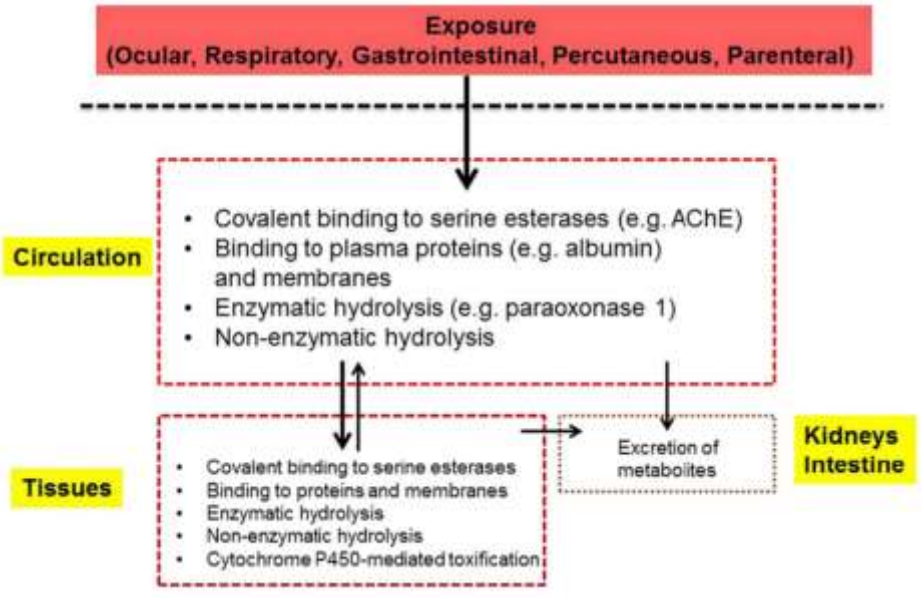


Figure 3. Toxicokinetic of organophosphorus insecticides ***(15).***

Distribution:

OPs are usually well distributed throughout the body tissues, specifically in fatty tissues because of their lipophilic characteristics. The bioavailability of the OPs and exposure pathway determine the amount of the parent compound entered the circulation after consumption ***(28).***

Some OPs, such as diazinon, fentione, and methyl parathion, are highly lipid soluble, allowing them to accumulate in fat and cause delayed toxicity due to late release. Delayed toxicity can also occur uncommonly with other OPs, particularly dichloropentione and demton methyl ***(30).***

Metabolism (Figure 4):

The biotransformation processes of OPs have two outcomes: (i) toxic activation, when the product of the reaction is more soluble in water and more reactive; (ii) detoxication reactions, when the products are less toxic. The liver is the main site for metabolic activation and detoxification reactions ***(28).***

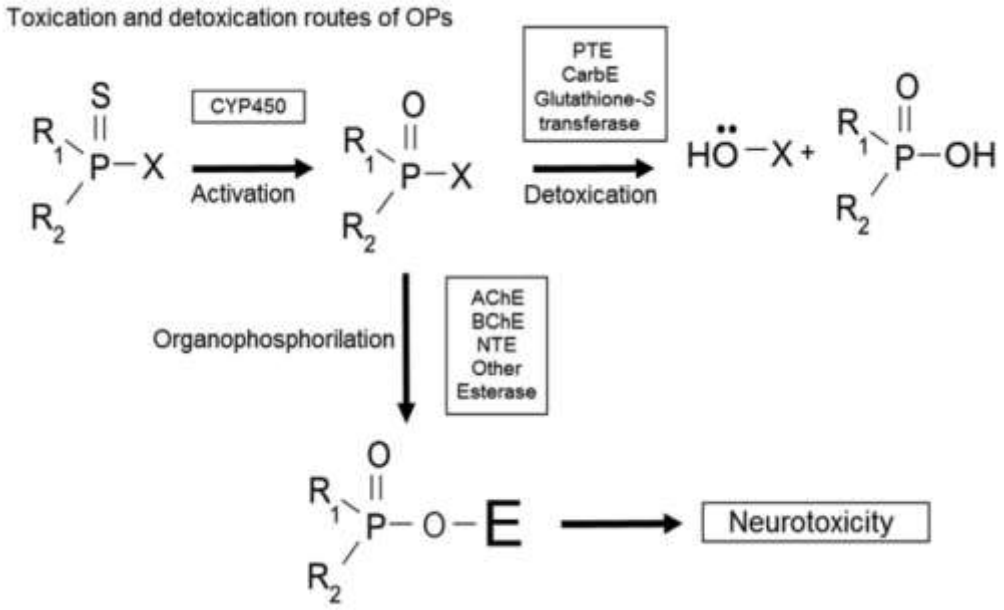


Figure 4. Enzymatic systems involved in organophosphorus compounds (OPs) biotransformation. AChE: Acetylcholinesterase; BChE: butyrilcholinesterase; CarbE: carboxylesterases; NTE: neuropathy target esterase; PTE: phosphotriesterase ***(28).***

Breakdown occurs mainly through liver hydrolysis, and rates of hydrolysis differ commonly from one compound to another. In those organophosphates where breakdown is relatively slow, important temporary storage in body fat may happen ***(31).***

organophosphates may be detoxified by other routes including catalytic hydrolysis by A-esterases (phosphotriesterases), such as paraoxonase (PON1), which hydrolyses the oxons of organophosphates including chemical warfare nerve agents ***(32).***

In 1984, it was reported that the human serum albumin has a role in OPs detoxication. Recent studies have showed that the OPs chlorpyrifos-oxon, diazoxon, O-hexyl O-2,5-dichlorophenyl phosphoramidate (HDCP), paraoxon, and soman are degraded by albumins from various species. The hydrolysis process is based on the phosphorylation of tyrosine ***(28).***

Excretion:

Elimination of metabolites occurs mostly in urine with lower amounts in feces and exhaled air ***(33).*** Their delayed excretion in urine is determined by their lipophilicity. More stable substances from degradation are easily eliminated in urine and may be useful as exposure indicators ***(28).***

Mechanism of organophosphorus insecticides toxicity (Figure 5):

Three major processes are involved in the pathophysiological mechanisms of organophosphorus poisoning: cholinergic with anticholinesterase effects, membrane toxicity, and pro-oxidant effect ***(30).***

To inhibit AChE, the phosphorus atom has to create a double bond with oxygen. This is known as a P = O moiety. Some organophosphates have this, therefore they are immediately effective AChE inhibitors and thus highly hazardous to mammals, such as, the nerve agents sarin and soman ***(34).***

The basic mechanism of toxicologically significant action of OPs and nerve agents is the covalent attachment to the active site serine OH-group at the base of a deep gorge of the pivotal enzyme acetylcholinesterase ***(15).***

Two types of cholinesterase are present in the human body, a) true cholinesterase (acetylcholinesterase), which appears in higher concentration in central nervous system and the outer membrane of red blood cells. b) pseudo-cholinesterase (butyrylcholinesterase), which presents in plasma, liver, cerebrospinal fluid, and glial cells ***(35).***

Organophosphorus insecticides have the capability to bind irreversibly to AChE and stop the breakdown of Acetylcholine (ACh). Liberation of ACh leads to over-stimulation of both muscarinic and nicotinic receptors which are widely dispersed throughout the body ***(12).***

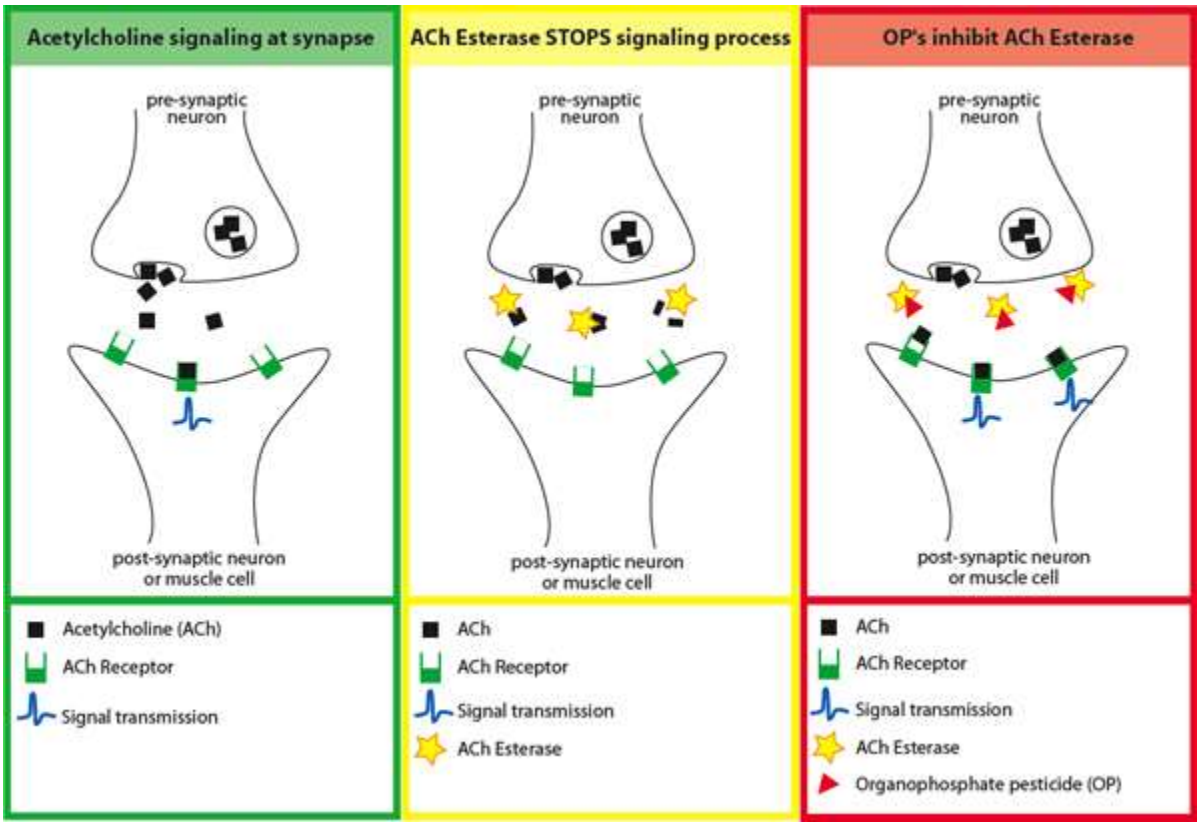


Figure 5. The mechanism of action of OPs ***(36)***.

OPs exert their mechanism of toxicity by the covalent organophosphorylation of esterases and cholinesterases. The resulting phosphorylated enzyme is usually very slowly cleaved and remains inhibited. In some cases, the recovery by spontaneous reactivation may occur at a significant speed or be forced by nucleophilic reagents such as fluoride or oximes. Besides, the phosphoryl enzyme can undergo a dealkylating reaction called aging **(Figure 6).** The negative charge of the aged phosphoryl group is more stable and this makes the enzyme not reactivable anymore, either spontaneously or by a reactivating agent ***(28).***

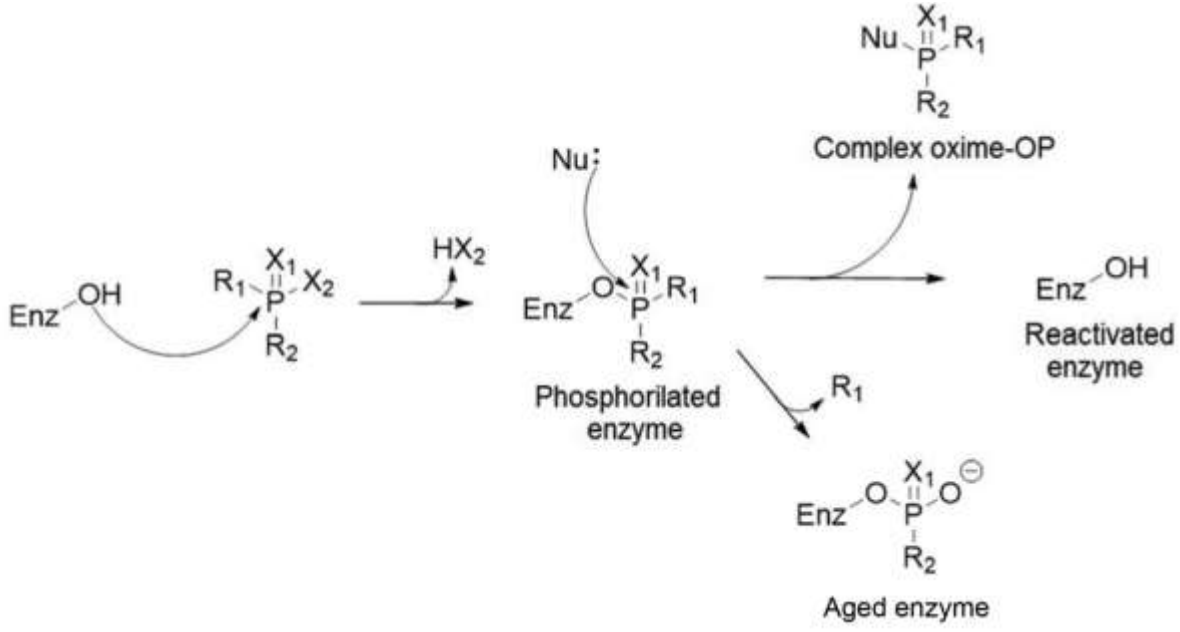


Figure 6. General scheme for the inhibition/aging of esterases and cholinesterases by organophosphorus compounds (OPs) and its reactivation through a nucleophilic agent ***(28).***

Another mechanism of action is that OPs can activate signalling pathways for oxidative stress through the production of reactive oxygen species (ROS), resulting in further tissue damage through the induction of lipid peroxidation, protein oxidation, and cell apoptosis ***(30).***

Types of acetylcholine receptors (Table 1):

1) Nicotinic receptors

There are two kinds : central and peripheral. The central nicotinic receptors are of the neuronal subtype (Nn or N2); this subtype is also present in the adrenal medulla and sympathetic and para-sympathetic ganglia of the peripheral nervous system (PNS). The peripheral nicotinic receptors (N1 or Nm) are present in the neuromuscular junction (NMJ) ***(37).***

2) Muscarinic receptors

The muscarinic receptor is a single subunit transmembrane spanning G-protein-coupled receptor derived from one of the five distinct subunits (M1–M5), derived from separate genes. Muscarinic

receptors located post-synaptically on end organs innervated by post-ganglionic parasympathetic neurones and also in cortical regions of the central nervous system (CNS). They are also located pre-synaptically at NMJ ***(38).***

Table 1. Symptoms and signs of organophosphate poisoning based on receptors involved ***(37).***

Type of receptor	Receptor sub-type	Action on	Manifestation
Nicotinic receptor stimulation	N1 (Nm) receptors	Neuromuscular junction	Weakness, fasciculations, cramps, paralysis
	N2 (Nn) receptors	Autonomic ganglia Adrenal medulla	Tachycardia, hypertension
Muscarinic receptor stimulation	M1-M5*	Central nervous system	Anxiety, restlessness, ataxia, convulsions, insomnia Dysarthria, tremors, coma, respiratory depression Circulatory collapse
	M2 receptor	Heart	Bradycardia, hypotension
	M3, M2 receptor*	Pupils	Blurred vision, miosis
	M3, M2 receptors*	Exocrine glands	Respiratory-rhinorrhea, bronchorrhea Gastrointestinal-increased salivation, diarrhea Ocular-increased lacrimation Others-excessive sweating
	M3, M2 receptors*	Smooth muscles	Bronchospasm, abdominal pain, urinary incontinence

Clinical picture of organophosphorus poisoning:

Manifestation of OP poisoning is classified as the muscarinic, nicotinic, and central nervous system. Muscarinic receptor overstimulation causes parasympathetic excitation, which can include miosis, bradycardia, and bronchorrhea. The nicotinic reaction is characterized by muscle fasciculation, cramping, and weakness, whereas central nervous system effects cause loss of consciousness, respiratory depression, and convulsions ***(39).***

These clinical features determine the severity of poisoning and have prognostic significance ***(24).***

Normally, muscarinic hyperstimulation occurs early in OP exposure followed later by nicotinic hyperstimulation. The typical sequence of events includes hypersalivation, sweating, lacrimation and other muscarinic effects, with muscle fasciculations and motor abnormalities following with gradual onset of coma and grand mal seizures ***(29).***

Symptoms and signs can occur within 5 minutes following massive ingestion and almost always within 12 hours. Muscarinic symptoms rarely appear after 24 hours after ingestion, but they may reappear if oximes and atropine treatment are withdrawn too quickly ***(37)***.

Organophosphorus poisoning can cause a variety of syndromes, including acute cholinergic crises, intermediate syndrome (IMS) which can proceed from ~20% of first, and OP-induced delayed neuropathy. Because of high mortality risk, both the acute cholinergic crises and the intermediate syndrome are best managed in an intensive care unit, unless the poisoning has been very mild ***(40).***

I. Acute onset manifestations

Acute symptoms and signs are caused by muscarinic, nicotinic, and central receptor effects. Muscarinic symptoms of salivation and bronchorrhea that originally predominate may cause dizzy

patients to drown in their secretions. Acute muscarinic impacts on the heart (e.g., bradycardia, hypotension) can be life-threatening. Nicotinic impacts of muscle weakness can lead to respiratory distress. In addition, severe major impacts of restlessness, agitation, confusion and sometimes convulsions further compromise the airways and breathing and rise the danger of aspiration and hypoxia. As many of these impacts are reversed by atropine, early and suitable medical attention is essential ***(37)***.

II. Delayed onset manifestations

IMS refers to the health effects noticed in patients who survive to acute high-level exposure to the Organophosphorus nerve agents ***(41).***

IMS is characterized by paralysis of the proximal limb muscles, neck flexors, motor cranial nerves, and respiratory muscles. It begins 24–96 hours after poisoning, with weakness lasting up to 18 days. Extremely lipophilic OPs have been shown to cause delayed onset intermediate syndrome after 114 hours of exposure. The delayed onset of symptoms could be attributed to cholinesterase redistribution and re-inhibition. Electromyographic tests revealed a neuromuscular junctional dysfunction ***(37)***.

The mechanism behind IMS is believed to be due to prolonged inhibition of AChE and where AChE inhibition is relatively short lived. Gradual decline in AChE activity associated with exposure to certain OPs or a syndrome of acute recovery followed by gradual decline due to leaching of the compound from tissue stores and conversion into active oxon (e.g. diclorvos, fenthion) appears to be the contributing factor in many cases of IMS ***(29).***

III. Late onset manifestations

OPs poisoning may be followed weeks later by an Organophosphorus-induced delayed polyneuropathy (OPIDP) due to inhibition of neuropathy target esterase in axons. Neuropathy target esterase catalyzes the deacylation of phosphatidylcholine—the major phospholipid of eukaryotic cell membranes—to soluble products. Its inhibition causes paralysis, with swelling and degeneration of distal long axons in the legs and spinal cord. OPIDP can cause respiratory failure through phrenic nerve involvement ***(42).***

Signs and symptoms of OPIDP include tingling of the hands and feet, followed by sensory loss, progressive muscle weakness and flaccidity of the distal skeletal muscles of the lower and upper extremities, and ataxia. These effects appear 2–3 weeks after exposure, when eventual signs of acute cholinergic toxicity have faded ***(14).***

OPIDP has four different phases: latent phase, progressive phase, stationary phase, and improvement phase. The latent period is the delay time ranging around 10 days to 3 weeks between OP exposure and the onset of neurological manifestations. The progressive phase is characterized by symmetric cramping, burning, flaccid paralysis,and sometimes urinary and bowel irregularities. During the stationary phase, neurological symptoms persist. As the patient enters the improvement phase, the sensory symptoms resolve prior to motor symptoms. The peripheral nervous system regenerates during this phase ***(43).***

Nerve biopsy may reveal signs of axonal degeneration with secondary demyelination. Recovery is usually complete, especially in young people. However, mild weakness with a rise in the vibration threshold may persist for 2 years following acute poisoning *(37).*

Causes of death

Death from OPs can occur within few hours if not treated. The main causes are respiratory failure, pulmonary edema, and cerebral hypoxia ***(44).***

Three mechanisms are suggested for respiratory failure occurring within few hours of acute cholinergic exposure: respiratory center depression in the ventrolateral medulla, respiratory muscle weakness, and immediate lung impacts (bronchospasm, bronchorrhea). Bronchorrhea is the result of neuronal and non- neuronal cholinergic stimulation of mucus glands, cilia and periciliary fluid-producing cells ***(42)***.

Aspiration pneumonia is very predominant. Other pulmonary function modifications connected with OPs toxicity include decreased dynamic lung compliance and increased complete pulmonary resistance. Respiratory effects are generally more severe in elderly patients with history of respiratory diseases *(45).*

The death rate could reach 40% even with adequate treatment ***(46).*** Other complications related to organophosphorus poisoning are motor neuropathy, pulmonary edema, pneumonia, arrhythmia and renal failure. Pancreatitis can occur in organophosphorus poisoning and reported to be in 12.8 % of cases ***(47).***

OP exposure has a major effect on the cardiac function. It appears in the form of hypotension, bradycardia, or tachycardia, resulting from several mechanisms, such as autonomic disturbances, consequences of hypovolemia or hypoxia, peripheral vasodilatation, and direct myocardial damage. Other life threatening cardiac conditions appear in form of ventricular tachyarrhythmias, torsades de pointes, and various electrocardiography (ECG) abnormalities such as QT interval prolongation These abnormalities are strongly confounded by the hypoxia and hypovolemia associated with cholinergic crisis and more commonly reported before atropinization ***(48).***

Renal failure may be the cause of death in some OP cases. Acute kidney injury (AKI) has been seen with OP poisoning. The main mechanism by which OPs can cause AKI has been debated. Different mechanisms have been suggested, such as oxidative stress, direct damage to the renal tubules, rhabdomyolysis, and hypovolemia due to dehydration ***(49).***

Studies have shown that the solvents used in OP preparation may have major toxic effects. In many occasions, solvents such as cyclohexanone are used to improve storage and solubility of OPs, and these themselves have a toxic effect and can cause pulmonary oedema due to aspiration . It is also likely that there is a central effect of the solvents on respiratory and cardiovascular centres by directly altering GABAergic inhibitory neurotransmission and affecting membrane properties of neurones causing direct respiratory depression ***(29).***

Diagnosis of organophosphorus insecticides poisoning:

Clinical signs are used mainly to make a diagnosis. Measurement of pseudo-cholinesterase is the most evident test of Organophosphorus poisoning. Early antagonism of Organophosphorus poisoning as evidence suggested, should be accompanied by better outcome ***(39).***

According to ***Moussa et al. (9);*** diagnosis of acute Organophosphorus poisoning was based on the following criteria:

a) History of exposure or contact.

b) Characteristic clinical signs and symptoms.

c) Improvement of signs and symptoms following treatment with atropine and pralidoxime.

d) Decrease of true or pseudo-cholinesterase activity.

Clinical diagnosis

Clinicians must have a high level of suspicion when challenged with comatose patients with characteristic insecticidal odor, myosis, increased airway secretions, gastrointestinal complaints, muscle fasciculations, and respiratory distress. Delay in finding and seeking medical help for poisoning, insufficient airway management, severe comorbid medical circumstances, and the intensity of OP contribute to the mortality of these patients ***(50).*** Patients are classified into 3 grades (**Table 2).**

Table 2. Severity of poisoning was graded using modified Dreisbach's classification ***(51).***

Appendix 1: Dreisbach's classification showing severity of poisoning	
Grade	**Symptoms**
Mild	Nausea, vomiting, diarrhoea, sweating
Moderate	Lacrimation, salivation, miosis, fasciculation
Severe	Incontinence, apnoeic spells, ARDS, areflexia seizures, coma

ARDS – Acute respiratory distress syndrome

Prognostic assessment and estimation are key to predicting outcomes. Therefore, multiple descriptive and prognostic evaluation scales (scoring systems) have been developed and used in the emergency department to predict the severity and mortality rate of OPs poisoning. A simple system based on clinical features is likely to be most useful in low-income countries where most of poisoning occurs ***(52).***

Peradeniya Organophosphorus poisoning (POP) scale is a simple and effective system to determine the severity of acute Organophosphorus poisoning **(Table 3)**. Common clinical manifestations of poisoning are selected as parameters each is assessed on a three-point scale varying from 0 to 2. The score is obtained at initial presentation before any medical intervention and it represents the muscarinic, nicotinic and central effects of acute cholinergic manifestations. The overall score of 0 to3 considered as mild poisoning, 4 to 7 as moderate poisoning and 8 to 11 as severe poisoning ***(53).***

Table 3. Peradeniya Organophosphorus Poisoning (POP) Scale, (0–3, Mild Poisoning; 4–7, Moderate Poisoning; 8–11, Severe Poisoning) ***(54).***

Parameter	Findings	Scale
Pupil size	≥ 2 mm	0
	< 2 mm	1
	Pinpoint	2
Respiratory rate	< 20/ minute	0
	≥ 20/minute	1
	≥ 20/minute with cyanosis	2
Heart rate	> 60/ minute	0
	41-60/minute	1
	< 40/minute	2
Fasciculations	None	0
	Present, ± generalized ± continues	1
	Both generalized & continuous	2
Consciousness level	Conscious & oriented	0
	Impaired verbal response	1
	No verbal response	2
Seizures	Absent	0
	Present	1

Laboratory analysis

Laboratory evidence of Organophosphorus Poisoning is usually confirmed by assessing the decline in acetylcholine esterase activity ***(22).***

There are two types of enzyme: BuChE, which is the pseudo type of the enzyme, and AChE, which is the true type of the enzyme located in the red blood cells. Despite the differences between the two types of cholinesterases, both are similarly under the influences of individual characteristics and diseases ***(55).***

OPs inhibit BuChE , but this does not contribute to the adverse clinical effects. The reference range is 3,000–7,000 U/L, but it can be decreased due to other reasons, including genetic deficiency or comorbidities such as liver disease. The degree of BuChE inhibition and time-course of regeneration varies between different OPs so it is less useful for prognosis ***(56).*** BuChE is more sensitive, but less specific than AChE, so at present it is used as a marker of OP exposure ***(57).***

Kumar et al. (58) reported that, The severity of poisoning was defined as per :

• Latent: BuChE level >50% of normal value.

• Mild poisoning: BuChE level 20-50% of normal value.

• Moderate poisoning: BuChE level 10-20% of normal value.

• Severe poisoning: BuChE level is < 10% of normal value.

On the other hand, ***Biswas et al. (59)*** reported that, BuChE level, which is expected to fall is not specific, does not correlate well with the severity of poisoning, and cannot be used as a prognostic indicator.

During exposure to OP compounds, decrease in BuChE activity usually falls first, followed by the decrease in AChE activity. The BuChE activity usually recovers before AChE activity, returning to normal within a few days after a mild exposure in the absence of a repeated exposure ***(60).***

AChE correlates with other physiological measures of the severity of poisoning, including NMJ function ***(57).***

Levels of nerve AChE inhibition of approximately over 70% lead to the accumulation of ACh in synaptic clefts of neuromuscular junctions, which causes neuromuscular block and respiratory failure in severe cases ***(28).***

Pharmacological diagnosis

The diagnosis of acute OP poisoning is supported by the response to intravenous (IV) atropine, for example 0.6 to 1 mg IV in an adult; here, if the symptoms improve then it is likely that they have been exposed to an OP. However, due to the lack of studies, interpreting the sensitivity and specificity of this trial can be challenging, particularly in cases of severe poisoning. Therefore, further studies are needed to address this issue ***(61).***

Treatment of poisoned cases:

OPs poisoned patients should be treated according to the severity of the poisoning. Mild cases should be treated with monitoring, supportive care and atropine therapy. Moderate cases with supportive treatment, atropine and diazepam should be administered. Consider the need for oxime if there is no significant recovery within few hours of complete atropinisation. Supportive treatment (mechanical ventilation), atropine, oxime and diazepam should be used in severe cases. The immediate beneficial effect of oximes cannot be expected at high, and constant levels of free poison in the blood, however, this should not prevent us from continuing oxime use in such cases ***(62)***.

1) Stabilization (Table 4)

Maintaining opened airway is very important including temporising manoeuvres and secretions suction. High flow oxygen is necessary to maintain breathing and consider also atropine administration. The initial treatment of hypotension includes replacement of volume lost by fluids using normal saline , if persist , infusions of vasopressors such as noradrenaline are required. Neurological Assessment of the Glasgow Coma Score (GCS) is useful. Seizures are un common but if occurred , administration of benzodiazepines is necessary ***(61).***

Acute OPs poisoning patients usually experience respiratory distress. In these situations, 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 ***(63).***

Table 4. Overview of the initial assessment of a patient with acute OP poisoning ***(57).***

System	Clinical observation	Signs of compromise
Airway	Listen for noises, inspection of the oropharynx	Snoring, gurgling, vomit in oropharynx, hypersalivation
Breathing	Respiratory rate, auscultation, oxygen saturations	Tachypnoea, wheeze, generalised crepitations, cyanosis or hypoxia on pulse oximetry, accessory muscle use
Circulation	Pulse rate, blood pressure, peripheral perfusion including capillary refill, jugular venous pressure	Hypotension, bradycardia; or hypertension, tachycardia
Neurological	Pupil size and response to light, inspect muscle and examine function (tone, power, reflexes, plantar response)	Miosis (constricted pupils), fasciculations, seizures, hyper-reflexia, decreased level of consciousness

2) Decontamination

The method of decontamination involves removal of affected clothes and washing the skin and hair with soap and water. Oral activated charcoal can be offered to co-operative patients who present within 1–2 h of ingestion. Gastric lavage using a naso or orogastric tube can be performed if the airway is protected (intubation), within 1–2 h of ingestion. Forced emesis is not recommended due to the risk of aspiration ***(57).***

3) Antidotal treatment

Time of antidote administration seems to be a key factor in patient´s outcome ***(39).***

- **Atropine**

The first-line antidotes in acute OP poisoning are antagonists of muscarinic ACh receptors**.** Atropine is the most widely used and the initial dose is 2 to 5 mg for adults IV (or 0.05 mg/kg in a child). If no response to the treatment, the dose should be doubled every 3 to 5 minutes until respiratory secretions have cleared and there is no bronchoconstriction. A decrease in mortality and less adverse effects is reported when this regimen was used ***(61).***

Atropine can reverse the muscarinic symptoms, cross the blood brain barrier (BBB) and counteracts the effects of Ach accumulation in CNS. However, it is not effective on nicotinic receptor medicated manifestations ***(64).***

A patient is considered adequately atropinised when the following minimum criteria are achieved: pulse > 80 beats/min, systolic blood pressure > 100 mmHg, chest clear on auscultation. Clinical features of atropine overdosing include an agitated delirium, urinary retention and fever. These can progress to dehydration, rhabdomyolysis, acute kidney injury and physical injuries in the absence of supportive care ***(57).***

Sweating is one of the first signs to resolve with atropine administration; by contrast, the reversal of pupil constriction can be delayed and should not be used to guide atropine administration ***(65).***

Other anti-muscarinic agents are also available, including glycopyrrolate and hyoscine (hydrochloride or butylbromide). The primary difference between these agents is the extent to

which they cross the blood–brain barrier. Atropine and hyoscine hydrochloride distribute to the brain to a more significant extent than glycopyrrolate and hyoscine butylbromide. A possible indication for using glycopyrrolate or hyoscine butylbromide is in cases of milder OP poisoning to limit the severity of an anticholinergic-induced delirium. However, in case of an acute cholinergic crisis, atropine is recommended rapidly ***(57).***

Oximes (reactivators)

The key role of oximes is to restore normal cholinergic transmission at the NMJ. Two oximes are in clinical use for the treatment of OP poisoning. Pralidoxime (PAM) is a monopyridinium oxime and obidoxime (LuH-6, Toxogonin) is a bispyridinium oxime. Obidoxime is more potent than pralidoxime, allowing administration of lower doses of obidoxime to achieve similar degrees of AChE reactivation ***(66).***

The mechanism of AChE reactivation is based on the nucleophilic attack of the reactivator hydroxyiminomethyl (oxime) moiety towards the OP moiety of the phosphorylated AChE. The covalent bond between OP and AChE serine is cleaved, reactivator-OP complex (phosphorylated reactivator) is formed, and the enzyme is liberated ***(67).***

The potential therapeutic window for the administration of an AChE antidote is determined by the "aging process," which is the inactive state of AChE (when it is attached to the OP). If this occurs, there is a non-enzymatic removal of one alkyl side chain of the phosphoryl moiety, leaving a hydroxyl group in its place. Once the AChE is "aged," regeneration is not possible ***(7).***

Oximes should be administered as soon as possible to prevent ageing and promote adequate reactivation of AChE. However, a beneficial response has been reported even after 24 hours of exposure ***(51).***

Oximes are associated with multiple side effects, such as dizziness, blurred vision, muscle weakness, the inhibition of patients' respiration on rapid administration, cardiac arrhythmia, and repeated asystole. Liver function abnormalities, as well as hepatitis, have been reported with high cumulative doses of atropine and obidoxime. Besides, some studies have showed increased need for intensive care and ventilation requirements with the use of oxime, although it has not been conclusively proven ***(59).***

Other oximes, including trimedoxime, HI-6 and HLö-7, have been developed but have not yet been introduced into widespread clinical use. This is probably because their development has focused on OP nerve agent poisoning in industrialized countries rather than the much more common OP insecticide poisoning ***(65).***

- **Diazepam**

Benzodiazepines are recommended as first-line therapy in seizures ***(68).***

Benzodiazepines may also reduce discomfort associated with fasciculations and settle agitation and delirium from the OP or treatment with atropine. Prophylactic benzodiazepine use has also been proposed. They may improve respiratory function or prevent neurological injury associated with central cholinergic stimulation. Some centres have advocated IV diazepam up to 40 mg/day for the first 24–48 h in severely poisoned patients, for example those requiring intubation ***(57).***

- **Sodium bicarbonate**

The mechanism of action in OP poisoning is unconfirmed but potential factors include enhanced elimination by hydrolysis, volume expansion and improved tissue perfusion, improved efficacy of oximes and a direct effect on neuromuscular function ***(69).***

Intravenous infusion of sodium bicarbonate (5 mEq/ kg in 60 min followed by 5-6 mEq/kg/day) helps in moderate alkalinization (blood pH between 7.45 and 7.55) in OP poisoning, which has been shown to have beneficial effects ***(70).***

- **Magnesium Sulfate**

Magnesium decreases the release of synaptic acetylcholine by blocking calcium channels. Animal studies have suggested an advantage in minimizing cholinergic activation after OPs poisoning. Magnesium may also reduce the risk of ventricular tachycardia in patients with tachycardia due to nicotinic stimulation. Few clinical studies showed an increase in neuromuscular function with decreased mortality after magnesium sulfate administration, but these studies were not randomized and the methodology was uncertain*(71)*.

- **Clonidine**

Clonidine is an alpha-2-adrenergic receptor agonist that reduces acetylcholine synthesis and release from pre-synaptic terminals and decreases descending sympathetic transmission. Animal studies have suggested benefit of clonidine and atropine in sarin poisoning ***(72).*** A dose-finding study in patients with acute OP poisoning noted that adverse effects were not noted with an IV loading dose of 0.3 mg followed by 0.5 mg over 24 h ***(73).*** However **El-Ebiary et al. (74);** found that clinical outcome did not improve markedly in clonidine-treated patients compared to those treated with atropine and obidoxime only, in addition ,these patients associated with hypotention needing intervention, more studies needed to reach adefinitive conclusions about its efficacy.

- **Nicotinic Antagonists**

Nicotinic ACh receptors are located in the central nervous system, parasympathetic ganglia, the adrenal medulla and the motor endplate of the NMJ. Antagonists of these receptors may have multiple useful effects in patients with acute OP poisoning. Inhibition of nicotinic ACh receptors in the CNS may decrease neurotoxicity. Animal studies noted that two antagonists (named compounds 7i and 8) were neuroprotective against diisopropylfluorophosphate (a nerve agent) ***(57).*** However, many competitive nicotinic antagonists, such as tubocurarine, are highly toxic, resulting in a narrow therapeutic window which would make them unsuitable as a medical therapy for anticholinesterase poisoning ***(75).***

Beta-adrenergic agonists (salbutamol or albuterol)

Salbutamol might complement atropine during resuscitation by treating bronchospasm through beta-2 agonism. However, it might also work to increase fluid elimination from the lung. A nebulized dose of salbutamol might be able to access the alveolar epithelium and increase the rate of fluid removal in OP poisoning ***(65).***

4) Lipid emulsions

In recent years, intravenous lipid emulsions (ILE) have been used for the treatment of cardiotoxicity induced by lipid-soluble compounds including antipsychotics and antidepressants. They have also been suggested for OPs toxicity because some OPs are extremely lipid-soluble and

are formulated in lipid-soluble solvents. It is possible that ILE may redistribute the poison, but they may also increase absorption from the gut, thereby increasing toxicity ***(76).***

The exact mechanism of action remains unknown. The most widely accepted mechanism is the lipid sink model, i.e., lipophilic agents are extracted and contained in the ILE and thus unavailable for toxic effects on tissues. Another proposed hypothesis is the stabilization of the myocardium by the provision of free fatty acids, the predominant energy source of the heart) to the failing myocardium, thereby reversing cardiotoxicity ***(77).***

5) Organophosphate hydrolases

OPs are apolar compounds accumulating in fatty tissues, and can be eliminated by their conversion to water soluble compounds. The most effective way to increase their water solubility is hydrolysis to much more water soluble metabolites that may be removed in urine. Although these insecticides are able to hydrolyze spontaneously especially at high pH, the main route of their detoxification is enzymatic degradation by hydrolases generating less toxic metabolites ***(67).***

Among several enzymes that are capable of hydrolyzing OPs, organophosphate hydrolase (OPH) has been the most extensively studied because of its ability to hydrolyze a variety of OP neurotoxins including common insecticides and structurally similar chemical warfare agents such as sarin and soman ***(78).***

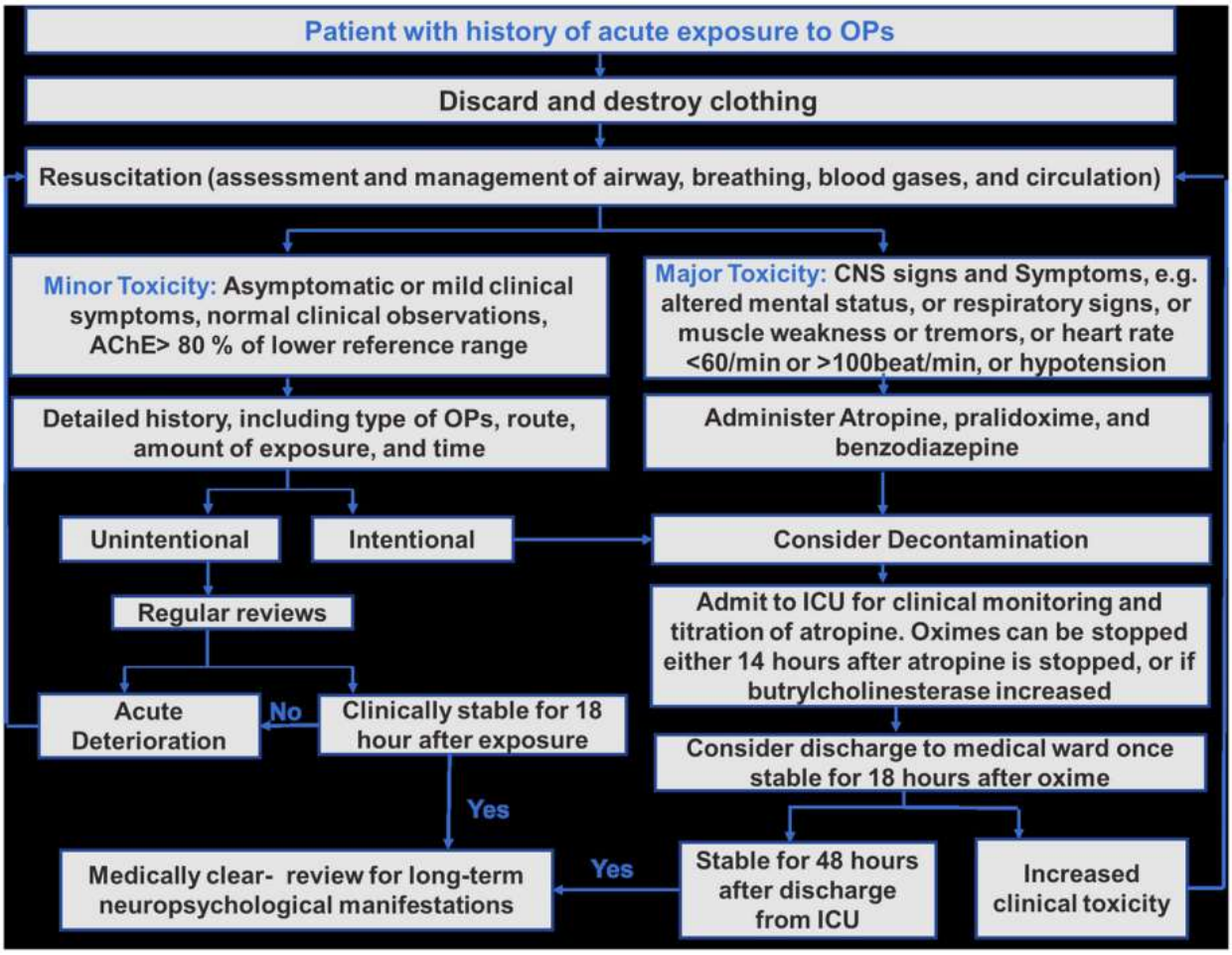
6) Current pre treatment.

Prophylactic treatments are important when there is high risk of exposure to OPs. One of them is AChE reversible inhibitors to hide the active site of AChE from the OPs. The most widely investigated is the carbamate pyridostigmine (the only FDA-approved substance for such pretreatment). This treatment maintains a sufficient amount of active AChE to preserve cholinergic transmission before intoxication and remain hidden from the OP during exposure. In this treatment, the dosage is extremely challenging. In addition, pyridostigmine does not readily cross the blood–brain barrier, leaving AChE of the central ***(7).***

Other prophylactic substance have been tested, such as physostigmine, tacrine, ranitidine and K-27. The most promising compound in this matter is the experimental oxime K-27, which is significantly more efficient than other tested cholinesterase inhibitors ***(7, 79).***

In the search of an AChE reversible inhibitor of the central nervous system, Huperzine A, a natural alkaloid, appears to have the greatest potential. However, this alkaloid is toxic at doses required for protection. A combination of isomers with lower toxicity could improve survival and reduce behavioral abnormalities ***(7).***

Table 5: Management of patients presenting with acute organophosphorus poisoning **(80).**



(AChE) acetyl cholinesterase, (CNS) central nervous system, (ICU) intensive care unit, (OPs) organophosphorus compounds

References:

1. Bondareva, L. & Fedorova, N. (2021): Pesticides: Behavior in agricultural soil and plants. Molecules, 26(17): 5370: 1-15.
2. Sarlak, Z., Khosravi-Darani, K., Rouhi, M., Garavand, F., Mohammadi, R. & Sobhiyeh, M. R. (2021): Bioremediation of organophosphorus pesticides in contaminated foodstuffs using probiotics. *Food Control*, *126*, 108006.
3. Karami-Mohajeri, S. & Abdollahi, M. (2011): Toxic influence of organophosphate, carbamate, and organochlorine pesticides on cellular metabolism of lipids, proteins, and carbohydrates: a systematic review. *Human & experimental toxicology*, *30*(9): 1119-1140.
4. Jayaraj, R., Megha, P. & Sreedev, P. (2016): Organochlorine pesticides, their toxic effects on living organisms and their fate in the environment. *Interdisciplinary toxicology*, *9*(3-4): 90-100.
5. Goel, A. & Aggarwal, P. (2007): Pesticide poisoning. *National medical journal of India*, *20*(4): 182-191.
6. Khayal, E. & Ahmed, M. (2019): Evaluating Chloropyrifos Induced Diabtes Mellitus, Pancreatic Toxic Effects in Adult Albino Rats and Whether This Insult Is Permanent or Temporary. *Ain Shams Journal of Forensic Medicine and Clinical Toxicology*, *33*(2): 92-103.
7. Alejo-González, K., Hanson-Viana, E. & Vazquez-Duhalt, R. (2018): Enzymatic detoxification of organophosphorus pesticides and related toxicants. *Journal of pesticide science*, *43*(1): 1-9.
8. Khalaf, M., Abbas, M. & Saleh, S. (2017): Pancreatic Dysfunction Associated With Severe Acute Anticholinesterase Insecticide Poisoning In Adults. *Ain Shams Journal of Forensic Medicine and Clinical Toxicology*, *28*(1): 144-148.

9. Moussa, M., Mohamed, S., Hilal, M., Elnabi, M. & Zaki, N. (2018): The role of APACHE II, SOFA, serum amylase and lipase in assessment of severity and outcome of acute organophosphorus poisoning. *Ain Shams Journal of Forensic Medicine and Clinical Toxicology*, *31*(2): 41-50.
10. Sepahi, S., Gerayli, S., Delirrad, M., Taghavizadeh Yazdi, M. E., Zare-Zardini, H., Bushehri, B. & Ghorani-Azam, A. (2023): Biochemical responses as early and reliable biomarkers of organophosphate and carbamate pesticides intoxication: A systematic literature review. *Journal of Biochemical and Molecular Toxicology*, *37*(3): e23285.
11. Eisa, H., Nomier, M. & Arafa, M. (2021): Amylase and Lipase Enzymes as Factors Affecting Acute Organophosphorous Poisoning Morbidity and Mortality. *Zagazig Journal of Forensic Medicine*, *19*(2): 76-99.
12. Adeyinka, A., Muco, E. & Pierre, L. (2023): Organophosphates. In *StatPearls* [Internet]. Retrieved from
13. https://www.ncbi.nlm.nih.gov/books/NBK499860/ (November 12, 2023).
14. Costa, L. G., Giordano, G., Guizzetti, M. & Vitalone, A. (2008): Neurotoxicity of pesticides: a brief review. Frontiers in Bioscience-Landmark, 13(4): 1240-1249.
15. Costa, L. G. (2018): Organophosphorus compounds at 80: some old and new issues. *Toxicological Sciences*, *162*(1): 24-35.
16. Worek, F., Wille, T., Koller, M. & Thiermann, H. (2016): Toxicology of organophosphorus compounds in view of an increasing terrorist threat. *Archives of toxicology*, *90*(9): 2131-2145.
17. Vale, A. & Lotti, M. (2015): Organophosphorus and carbamate insecticide poisoning. *Handbook of clinical neurology*, *131*: 149-168.
18. Balali-Mood, B. (2014): Chemistry and classification of OP compounds. In: *Basic and clinical toxicology of organophosphorus compounds.* By: Balali-Mood, M. & Abdollahi, M. (eds.), Springer-Verlag London, Chapter 1:1-23.
19. Walter, R. B. (2006): Biological Effects of Pesticides in Mammalian Systems. Annals of New York of Academy of Sciences, 160: 687-693.
20. Tucson, L. J. (2007): structure of organophosphate insecticides. In: Handbook of Toxicology. By Lindsay, M; Frank, D. and David, M. Springer-Verlag, New York, Heidelberg, and Berlin, pp:295-298.
21. Zghab, I., Trimeche, B., Besbes, M., Touboul, D., Martin, M. T. & Jannet, H. B. (2015): Synthesis and spectral studies of biologically active organophosphorus derivatives of substituted 4-(2-hydroxyphenylamino)-2 H-chromen-2-one. *Medicinal Chemistry Research*, *24*: 2167-2176.
22. Wu, X., Li, J., Zhou, Z., Lin, Z., Pang, S., Bhatt, P., ... & Chen, S. (2021): Environmental occurrence, toxicity concerns, and degradation of diazinon using a microbial system. *Frontiers in Microbiology*, *12*: 717286: 1-18.
23. Kumar, S., Agrawal, S., Raisinghani, N. & Khan, S. (2018): Leukocyte count: A reliable marker for the severity of organophosphate intoxication?. *Journal of Laboratory Physicians*, *10*(2): 185-188.
24. Ye, M., Beach, J., Martin, J. W. & Senthilselvan, A. (2013): Occupational pesticide exposures and respiratory health. *International journal of environmental research and public health*, *10*(12): 6442-6471.
25. Kamath, S. D. & Gautam, V. K. (2021): Study of organophosphorus compound poisoning in a tertiary care hospital and the role of Peradeniya Organophosphorus Poisoning scale as a prognostic marker of the outcome. *Journal of Family Medicine and Primary Care*, *10*(11): 4160–4167.
26. Roberts, J. R., Karr, C. J., Council on Environmental Health, Paulson, J. A., Brock-Utne, A. C., Brumberg, H. L., ... & Wright, R. O. (2012): Pesticide exposure in children. *Pediatrics*, *130*(6): e1765-e1788: 1-42.
27. Dündar, Z. D., Ergin, M., Köylü, R., Günaydın, Y. K., Özer, R. & Cander, B. (2015): Prognostic value of red cell distribution width in patients with organophosphate poisoning. *The Journal of Academic Emergency Medicine, 14*(2): 65-69.
28. Adeyinka, A., Muco, E. & Pierre, L. (2022): Organophosphates. In *StatPearls* [Internet]. Retrieved from
29. https://www.ncbi.nlm.nih.gov/books/NBK499860/
30. Mangas, I., Vilanova, E., Estévez, J. & França, T. C. (2016): Neurotoxic effects associated with current uses of organophosphorus compounds. Journal of the Brazilian Chemical Society, 27(5): 809-825.
31. Morris, C. M., Savy, C., Judge, S. J. & Blain, P. G. (2014): Acute toxicity of organophosphorus compounds. In: *Basic and clinical toxicology of organophosphorus compounds*. By: Balali-Mood, M. & Abdollahi, M. (eds.), Springer-Verlag London, Chapter3, 45-78.
32. Sobolev, V. E., Sokolova, M. O., Jenkins, R. O. & Goncharov, N. V. (2022): Molecular mechanisms of acute organophosphate Nephrotoxicity. *International Journal of Molecular Sciences*, *23*(16): 8855: 1-28.
33. Roberts, D. M. & Aaron, C. K. (2007): Management of acute organophosphorus pesticide poisoning. *Bmj*, *334*(7594): 629-634.

34. Peterson, M. W., Fairchild, S. Z., Otto, T. C., Mohtashemi, M., Cerasoli, D. M. & Chang, W. E. (2011): VX hydrolysis by human serum paraoxonase 1: a comparison of experimental and computational results. *PLoS One*, *6*(5): e20335: 1-7.
35. Vale, J. A. (1998): Toxicokinetic and toxicodynamic aspects of organophosphorus (OP) insecticide poisoning. *Toxicology Letters*, *102*: 649-652.
36. Costa, L. G. (2006): Current issues in organophosphate toxicology. *Clinica chimica acta*, *366*(1-2): 1-13.
37. Jokanovic, M. & Prostran, M. (2009): Pyridinium oximes as cholinesterase reactivators. Structure-activity relationship and efficacy in the treatment of poisoning with organophosphorus compounds. *Current Medicinal Chemistry*, *16*(17): 2177-2188.
38. George, N., Chauhan, P. S., Sondhi, S., Saini, S., Puri, N. & Gupta, N. (2014): Biodegradation and analytical methods for detection of organophosphorous pesticide: chlorpyrifos. *International Journal of Pure and Applied Sciences and Technology*, *20*(2): 79-94.
39. Peter, J. V., Sudarsan, T. I. & Moran, J. L. (2014): Clinical features of organophosphate poisoning: A review of different classification systems and approaches. *Indian journal of critical care medicine: peer-reviewed, official publication of Indian Society of Critical Care Medicine*, *18*(11): 735–745.
40. Saternos, H. C., Almarghalani, D. A., Gibson, H. M., Meqdad, M. A., Antypas, R. B., Lingireddy, A. & AbouAlaiwi, W. A. (2018) :Distribution and function of the muscarinic receptor subtypes in the cardiovascular system. *Physiological genomics*, *50*(1): 1-9.
41. Zobeiri, M. (2021): Serum amylase as a prognostic marker of organophosphate poisoning. *Journal of Injury and Violence Research*, *13*(2): 117–120.
42. Jokanović, M. (2018): Neurotoxic effects of organophosphorus pesticides and possible association with neurodegenerative diseases in man: A review. *Toxicology*, *410*: 125-131.
43. Karalliedde, L., Baker, D. & Marrs, T. C. (2006): Organophosphate-induced intermediate syndrome: aetiology and relationships with myopathy. *Toxicological reviews*, *25*(1): 1-14.
44. Hulse, E. J., Davies, J. O., Simpson, A. J., Sciuto, A. M. & Eddleston, M. (2014): Respiratory complications of organophosphorus nerve agent and insecticide poisoning. Implications for respiratory and critical care. *American journal of respiratory and critical care medicine*, *190*(12): 1342-1354.
45. Gautam, S., Sapkota, S., Ojha, R., Jha, A., Karn, R., Gajurel, B. P., ... & Shrestha, A. (2022): Delayed myelopathy after organophosphate intoxication: A case report. *SAGE Open Medical Case Reports*, *10*, 2050313X221104309. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9210101/ (Jun 16, 2022).
46. Lamb, T., Selvarajah, L. R., Mohamed, F., Jayamanne, S., Gawarammana, I., Mostafa, A., ... & Eddleston, M. (2016): High lethality and minimal variation after acute self-poisoning with carbamate insecticides in Sri Lanka–implications for global suicide prevention. *Clinical toxicology*, *54*(8): 624-631.
47. Hrabetz, H., Thiermann, H., Felgenhauer, N., Zilker, T., Haller, B., Nährig, J., ... & Eyer, F. (2013): Organophosphate poisoning in the developed world–a single centre experience from here to the millennium. *Chemico-biological interactions*, *206*(3): 561-568.
48. Carey, J. L., Dunn, C. & Gaspari, R. J. (2013): Central respiratory failure during acute organophosphate poisoning. *Respiratory physiology & neurobiology*, *189*(2): 403-410.
49. El-Sheikh, A. A., Khayal, E. E. S. & Allam, R. (2018): Human kidney injury molecule-1 and interleukin-18 as predictive markers of nephrotoxicity in acute organophosphorus poisoned patients in Zagazig University hospitals. *Journal of Toxicology and Environmental Health Sciences*, *10*(5): 34-43.
50. 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.
51. Zafar, R., Munawar, K., Nasrullah, A., Haq, S., Ghazanfar, H., Sheikh, A. B. & Khan, A. Y. (2017): Acute renal failure due to organophosphate poisoning: a case report. *Cureus*, *9*(7): e1523:1-8.
52. Lee, P. & Tai, D. Y. H. (2001): Clinical features of patients with acute organophosphate poisoning requiring intensive care. *Intensive care medicine*, *27*(4): 694-699.
53. Ahmed, S. M., Das, B., Nadeem, A. & Samal, R. K. (2014): Survival pattern in patients with acute organophosphate poisoning on mechanical ventilation: A retrospective intensive care unit-based study in a tertiary care teaching hospital. *Indian journal of anaesthesia*, *58*(1): 11–17.
54. Mahdavinejad, A., Pajoumand, A., Barari, B., Salimi, A. & Talaie, H. (2014): Lack of prognostic role for Glasgow coma scale, serum acetylcholinesterase and leukocyte levels in acute organophosphorus Toxicological ICU poisoned patients. *Life Sci J*, *11*(8s): 563-567.

55. Dubey, T. N., Yadav, S. & Kawre, K. K. (2016): Correlation of severity of organophosphorus poisoning as assessed by Peradeniya organophosphorus poisoning scale with serum amylase and CPK level. *International Journal of Contemporary Medical Research*, *3*(9): 2534-2537.
56. Hassan, N. A. & Madboly, A. G. (2013): Correlation between serum creatine phosphokinase and severity of acute organophosphorus poisoning: A prospective clinical study (2012-2013). *IOSR J Environ Sci Toxicol Food Technol*, *4*(5): 18-29.
57. Beltagy, D. M., Sadek, K. M. & Hafez, A. S. (2018): Serum β-glucuronidase activity as a biomarker for acute cholinesterase inhibitor pesticide poisoning. *Toxicology and Industrial Health*, *34*(12): 891-897.
58. Eddleston, M., Eyer, P., Worek, F., Rezvi Sheriff, M. H. & Buckley, N. A. (2008): Predicting outcome using butyrylcholinesterase activity in organophosphorus pesticide self-poisoning. *QJM: An International Journal of Medicine*, *101*(6): 467-474.
59. Roberts, D. M. & Brett, J. (2014): Clinical management of acute OP pesticide poisoning. In *Basic and Clinical Toxicology of Organophosphorus Compounds*. By: Balali-Mood, M. & Abdollahi, M. (eds.), Springer-Verlag London, Chapter 6: 141-175.
60. Kumar, S. V., Fareedullah, M. D., Sudhakar, Y., Venkateswarlu, B. & Kumar, E. A. (2010) :Current review on organophosphorus poisoning. *Archives of applied science Research*, *2*(4), 199-215.
61. Biswas, S., Ghosh, R., Mandal, A., Lapeña, J., Roy, D. & Benito-León, J. (2022): Is Serum Creatine Phosphokinase Level Useful to Predict the Severity of Organophosphate Poisoning?. *Medical research archives*, *10*(9): 1-11.
62. Tallat, S., Hussien, R., Mohamed, R. H., Abd El Wahab, M. B. & Mahmoud, M. (2020): Caspases as prognostic markers and mortality predictors in acute organophosphorus poisoning. *Journal of Genetic Engineering and Biotechnology*, *18*(1): 1-8.
63. Robb, E. L., Regina, A. C. & Baker, M. B. (2023): Organophosphate toxicity. In *StatPearls [Internet]*. Retrieved from
64. https://www.ncbi.nlm.nih.gov/books/NBK470430/ (November 12, 2023).
65. Singh, O., Javeri, Y., Juneja, D., Gupta, M., Singh, G. & Dang, R. (2011): Profile and outcome of patients with acute toxicity admitted in intensive care unit: Experiences from a major corporate hospital in urban India. Indian journal of anaesthesia, 55(4): 370–374.
66. Kazemi, M., Tahmasbi, A. M., Valizadeh, R., Naserian, A. A. & Soni, A. (2012): Organophosphate pesticides: A general review. *Agricultural science research journals*, *2*(9): 512-522.
67. Abd Alkareem, M. & Khater, A. (2019): Evaluation of Copeptin level and Peradeniya Score as Predictors of Severity and Outcome in Acute Organophosphorus Pesticides Poisoned Patients Admitted to the Poison Control Center Ain Shams University Hospitals (A Prospective Study). *Ain Shams Journal of Forensic Medicine and Clinical Toxicology*, *33*(2): 104-112.
68. 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.
69. Eyer, P. (2003): The role of oximes in the management of organophosphorus pesticide poisoning. *Toxicological reviews*, *22(3)*: 165-190.
70. Colovic, M. B., Krstic, D. Z., Lazarevic-Pasti, T. D., Bondzic, A. M. & Vasic, V. M. (2013): Acetylcholinesterase inhibitors: pharmacology and toxicology. *Current neuropharmacology*, *11*(3): 315-335.
71. 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.
72. Roberts, D. M., Fraser, J. F., Buckley, N. A. & Venkatesh, B. (2005): Experiences of anticholinesterase pesticide poisonings in an Australian tertiary hospital. *Anaesthesia and intensive care*, *33*(4): 469-476.
73. Narang, U., Narang, P. & Gupta, O. (2015): Organophosphorus poisoning: A social calamity. *Journal of Mahatma Gandhi Institute of Medical Sciences*, *20*(1): 46-51.
74. Basher, A., Rahman, S. H., Ghose, A., Arif, S. M., Faiz, M. A. & Dawson, A. H. (2013): Phase II study of magnesium sulfate in acute organophosphate pesticide poisoning. *Clinical Toxicology*, *51*(1): 35-40.
75. Wu-Fu, L. (1991): A symptomatological assessment of organophosphate-induced lethality in mice: comparison of atropine and clonidine protection. *Toxicology letters*, *56*(1-2): 19-32.
76. Perera, P. M., Jayamanna, S. F., Hettiarachchi, R., Abeysinghe, C., Karunatilake, H., Dawson, A. H. & Buckley, N. A. (2009): A phase II clinical trial to assess the safety of clonidine in acute organophosphorus pesticide poisoning. *Trials*, *10*: 1-9.

77. El-Ebiary, A. A., Gad, S. A., Wahdan, A. A. & El-Mehallawi, I. H. (2016): Clonidine as an adjuvant in the management of acute poisoning by anticholinesterase pesticides. *Human & Experimental Toxicology*, *35*(4): 371-376.
78. Tattersall, J. E. (2018): Anticholinesterase toxicity. *Current Opinion in Physiology*, *4*: 49-56.
79. Eddleston, M. (2019): Novel clinical toxicology and pharmacology of organophosphorus insecticide self-poisoning. *Annual review of pharmacology and toxicology*, *59*: 341-360.
80. Pannu, A. K., Garg, S., Bhalla, A., Dhibar, D. P. & Sharma, N. (2022): Lipid emulsion for the treatment of acute organophosphate poisoning: An Open-Label randomized trial. *Clinical Toxicology*, *60*(5): 602-608.
81. Theriot, C. M. & Grunden, A. M. (2011): Hydrolysis of organophosphorus compounds by microbial enzymes. *Appl Microbiol Biotechnol*, *89*(1): 35-43.
82. Lorke, D. E., Nurulain, S. M., Hasan, M. Y., Kuča, K. & Petroianu, G. A. (2014): Prophylactic administration of non-organophosphate cholinesterase inhibitors before acute exposure to organophosphates: assessment using terbufos sulfone. Journal of Applied Toxicology, 34(10): 1096-1103.
83. Badr, A. M. (2020). Organophosphate toxicity: Updates of malathion potential toxic effects in mammals and potential treatments. Environmental science and pollution research, 27(21), 26036-26057.