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AN INSIDE STORY OF ORGANO-PHOSPHOROUS POISONING: ITS LETHAL COMPLICATIONS

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ABSTRACT

According to World Health Organisation (WHO), An estimate of 2 million people attempt suicide every year worldwide. The incidence rate of organophosphorous poisoning were estimated 102,705 cases, among which india is the highest. Organophosphate is the commonest poison for accidental or suicidal deaths which are used for controlling the pest. Morbidity and mortality are due to insufficient respiratory management, delayed intubation, cardiac complications, aspiration pneumonia,weakness and neuropathy. Most organophosphates are highly lipid soluble compounds and are well absorbed from intact skin, oral mucous membranes, conjunctiva and the gastrointestinal and respiratory tracts. Organophosphorus compounds are acid-transferring inhibitors of cholinesterase. They cause cholinesterase to become firmly (and sometimes irreversibly) phosphorylated by which the action of cholinesterase will be inhibited. Accumulation of acetylcholine causes overstimulation of both muscarinic and nicotinic receptors, and subsequently disrupts the transmission of nerve impulses in both the peripheral and central nervous system. The complications of organophosphorous poisoning categorized into: Acute Cholinergic Crisis, intermediate syndrome, Delayed Polyneuropathy, cardiac menisfestation.The antidotes used for OP are Pralidoxime, Glycopyrolate, Atropine. Among which atropine is commonly used. Symptomatic treatment is necessary in the management of complications of organophosphorous poisoning.

KEYWORDS: organophosphorous, mechahism, pharmacokinetics, complications, treatment.

INTRODUCTION

According to World Health Organisation (WHO), An estimate of 2 million people attempt suicide every year worldwide. The incidence rate of organophosphorous poisoning were estimated 102,705 cases, among which india is the highest [1]. Organophosphate is the commonest poison for accidental or suicidal deaths which are used for controlling the pest [2]. Morbidity and mortality are due to insufficient respiratory management, delayed intubation, cardiac complications, aspiration pneumonia,weakness and neuropathy [3]. World Health Organization (WHO) has classified the toxic effects of pesticides into extremely hazardous (class Ia) to slightly hazardous (class III). Outcomes measured according to W.H.O classification of severity is shown in the table 1[5].

Table 1: WHO Classification for Severity

MILD	MODERATE	SEVERE
Anorexia, Headache, Dizziness, Weakness, Anxiety, Tremors of the tongue and the eye lids, Miosis, Impairment of vision	Nausea, Salivation, Lacrimation, Abdominal Cramp, Vomiting , Sweating , Slow pulse, Muscular tremors	Diarrhea, Pinpoint pupils and non-reactive pupils, Respiratory difficulty, Pulmonary edema, Cyanosis, Loss of sphincter, control, Convulsions, Heart block, Coma

PHARMACOKINETICS

- Most organophosphates are highly lipid soluble compounds and are well absorbed from intact skin, oral mucous membranes, conjunctiva and the gastrointestinal and respiratory tracts.
- They are rapidly redistributed to all body tissues. The highest concentrations are found in the liver and kidneys.
- It crosses blood-brain barrier and can produce potent effects on central nervous system
- Metabolism is mainly by oxidation and conjugation..
- The oxidative metabolites of malathion and parathion are active forms and are subsequently hydrolyzed into inactive metabolites.
- Elimination of organophosphorus compounds and its metabolites occur mainly via urine, bile and faeces.

MECHANISM OF ACTION OF ORGANOPHOSPHORUS COMPOUNDS

Acetylcholine (ACh) is the neurotransmitter released at all postganglionic parasympathetic nerve endings and at the synapses of both sympathetic and parasympathetic ganglia. It serves as a neurotransmitter in the central nervous system.ACh is hydrolyzed by acetylcholinesterase into two fragments: acetic acid and choline.Acetylcholinesterase is present in two forms: True acetylcholinesterase which is found primarily in the tissues and erythrocytes, and pseudocholinesterase which is found in the serum and liver.

Organophosphorus compounds are acid-transferring inhibitors of cholinesterase. They cause cholinesterase to become firmly (and sometimes irreversibly) phosphorylated by which the action of cholinesterase will be inhibited. Cleavage of the carbon-enzyme bond from ACh is complete in a few microseconds. However, the breaking of the phosphorus-enzyme bond requires a period varying from 60 minutes to several weeks, depending on the organophosphorus compound involved. OP's blocking acetyl choline esterase can be shown in the figure 1.

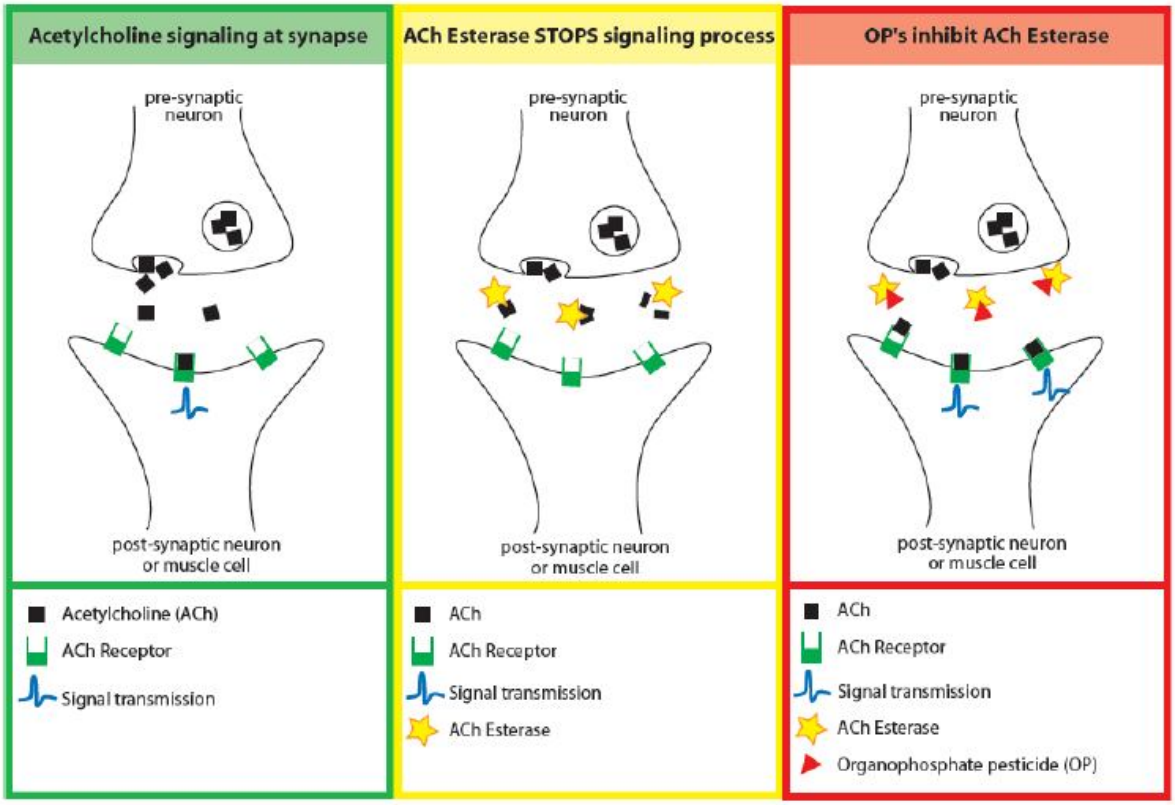

Fig 1: OP's blocking acetyl choline esterase

Reactivation of the inhibited enzyme may occur spontaneously (fig 2). The rate of reactivation will depend on the species, the tissue, and the chemical group attached to the enzyme. Reactivation may be enhanced by hydrolysis of the acid-radical-enzyme through the use of oximes (i.e. reactivating agents). Response to reactivating agent's declines with time; this process being caused by "ageing" of the inhibited enzyme. Ageing is probably the result of the loss of one alkyl or alkoxy group, leaving a much more stable acetylcholinesterase.The aged phosphorylated enzyme cannot be reactivated by oximes.

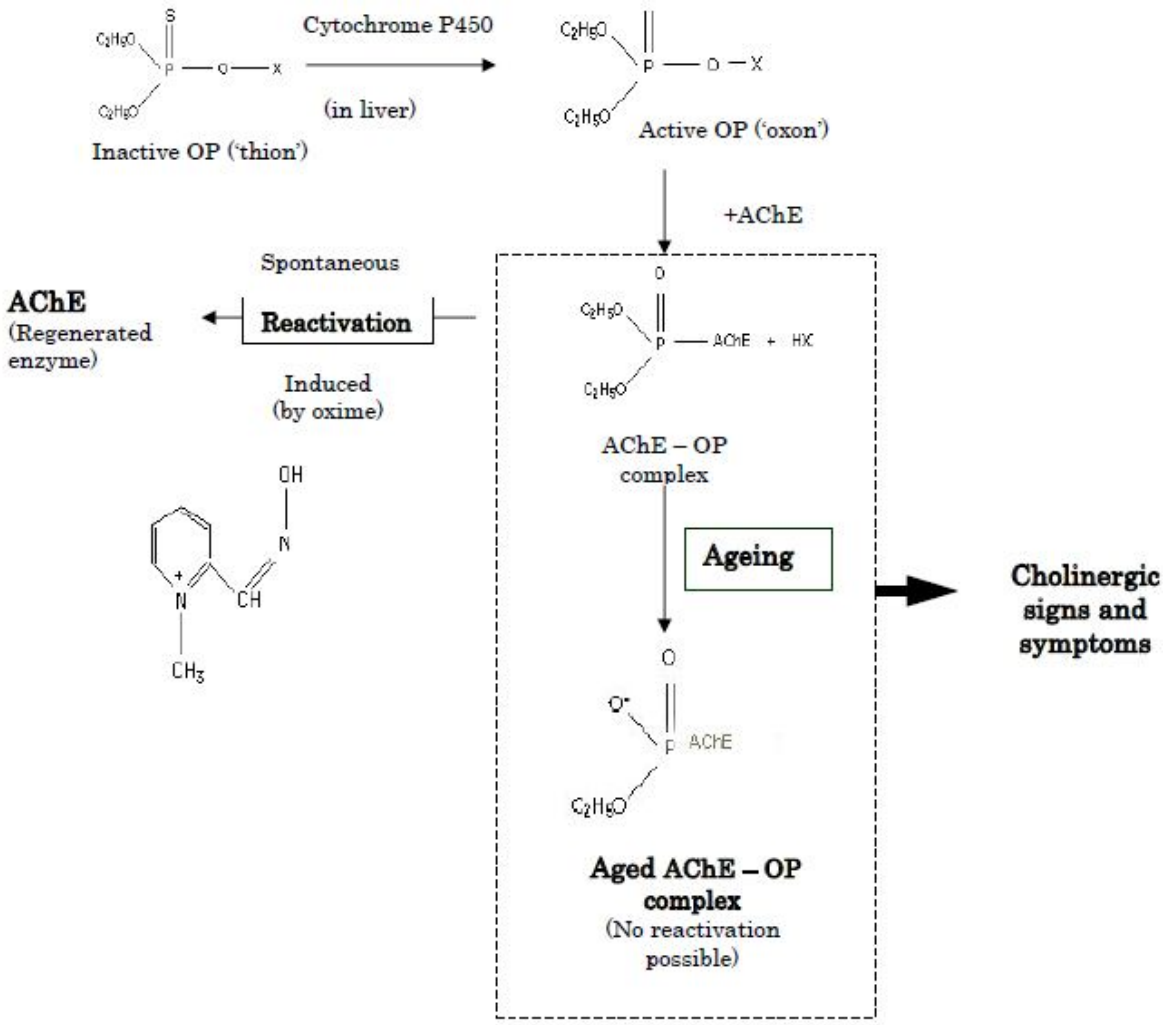

Figure 2: reactivation process

Accumulation of acetylcholine causes overstimulation of both muscarinic and nicotinic receptors, and subsequently disrupts the transmission of nerve impulses in both the peripheral and central nervous system [6][7].

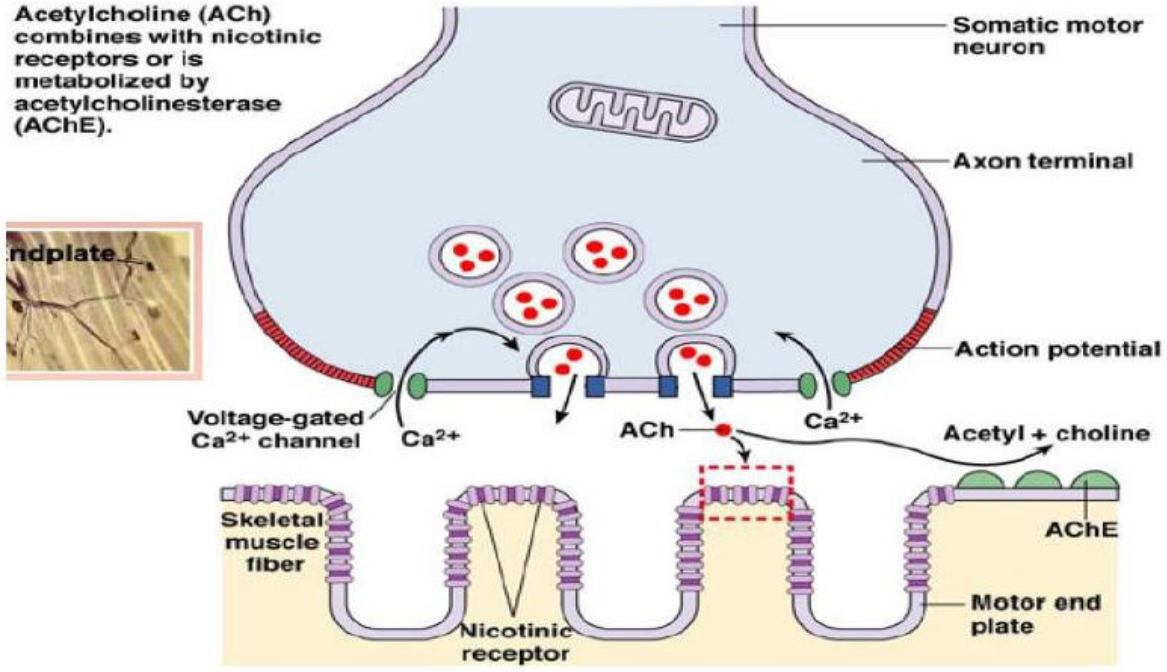

Figure 3: Showing neuromuscular junction where Cholinesterase are phosphorylated by the Phosphate end of Organophosphates, leading to accumulation of excessive Acetyl Chlorine with resultant effect on Muscarinic, Nicotinic and central nervous system

COMPLICATIONS OF ORGANOPHOSPHOROUS POISONING

Acute Cholinergic Crisis

The clinical features of acute OP poisoning reflect the degree of accumulation of acetylcholine (ACh) causing excessive stimulation of cholinergic receptors at various organs (acute cholinergic crisis). Acetylcholine is the principle neurotransmitter in various synapses in the human body: parasympathetic nervous system, autonomic ganglia, neuromuscular junction and central nervous system. Owing to the widespread distribution of cholinergic neurons in central and peripheral nervous can be hastened by adding nucleophilic reagentssystems, the signs and symptoms involve various organ systems. Depending on the severity of the exposure, the spectrum of the clinical presentation varies: the signs and symptoms may be mild, moderate or severe.

On the basis of the receptor stimulation, the acutemanifestations can be broadly divided into muscarinic, nicotinic, and central nervous system (CNS) effects. The important practical significance of this classification is that atropine only blocks muscarinic effects whereas

oximes reverse both the nicotinic and muscarinic effects by reactivating AChE atboth receptor sites because of their ability to reactivate inhibited AChE regardless of receptor type.

The two of the following mnemonics are used to demonstrate the muscarinic signs in organophosphorous poisoning

1. SLUDGE/BBB: Salivation, Lacrimation, Urination, Defecation, Gastric Emesis, Bronchorrhea, Bronchospasm, Bradycardia.
2. DUMBELS: Defecation, Urination, Miosis, Bronchorrhea / Bronchospasm /Bradycardia, Emesis, Lacrimation, Salivation.

The **nicotinic effects** includes: fasciculations, neuromuscular junction. Thismechanism is analogous to the depolarizing effects of succinylcholine in producing neuromuscular blockade. Nicotinic and muscarinic receptors also have beenidentified in the brain, and may contribute to central respiratory depression, lethargy, excitability, seizures and coma.

Intermediate syndrome

The intermediate syndrome is a distinct clinical entity that usually occurs 24 to 96 hours after the ingestion of an OP compound; after an initial cholinergic crisis but before the expected onset of delayed polyneuropathy.Approximately 10-40% of patients treated for acute poisoning develop this illness. This syndrome is characterized by prominent weakness of neck flexors, muscles of respiration and proximal limb muscles. Though originally seen with fenthion, dimethoate and monocrotophos, it is also seen in other OP compounds. The muscle weakness in intermediate syndrome may last up to 14 days and the condition regresses slowly if respiratory support is available. Though the exact pathogenesis of intermediate syndrome is unclear, the proposed mechanisms include persistent inhibition of AChE leading to functional paralysis of neuromuscular transmission, muscle necrosis, and oxidative free radical damage to the receptors.

Delayed Polyneuropathy

Delayed polyneuropathy is an uncommon consequence of severe intoxication or intermittent and chronic contact with OP pesticides as in occupational exposure. It is due to inhibition of neuropathy target esterase (NTE)enzyme in nervous tissues by certain OP compounds.Many locally available OPs have negligible NTE inhibitory effect except chlorpyrifos which causes intermediate degree of inhibition. Delayed polyneuropathy is often unrecognized in humans

and many times the clinical features are easily overlooked. Clinical manifestations are of distal symmetric sensory-motor polyneuropathy (distal weakness, parasthesia, ataxia, diminished or absent reflexes). The symptoms usually begin 2-5 weeks after exposure to the chemical, and may last for years.Apart from these well-defined neural syndromes, OP pesticides can also cause chronic neurotoxicity and behavioural impairment in some patients [8]

Cardiac manisfestation

The cardiac manifestations occur in a majority of affected patients and may range from innocuous electrocardiographic manifestations, such as sinus tachycardia, to life-threatening complications including cardiogenic pulmonary oedema. Repolarisation abnormalities, including ST segment elevation and T wave inversion as well as prolongation of the QTc interval, are among the most frequent cardiac manifestations of acute organophosphate poisoning . The mechanisms of organophosphate-induced cardiac toxicity are not fully understood. Aside from direct toxic effects of the organophosphate compounds, an increase in sympathetic and/or parasympathetic activity, hypoxaemia, acidosis and electrolyte abnormalities are thought to be involved in myocardial damage associated with organophosphate poisoning. Notably, experimental studies in isolated rat hearts suggested that obidoxime, a cholinesterase reactivator that is used as an antidote in cases of organophosphate poisoning, may even aggravate organophosphate-induced prolongation of the QT interval. The reported prevalence of various electrocardiographical changes in organophosphorouscompound is 89.1% [9].

Confirmation of Poisoning

If poisoning is probable, **treat the patient immediately. Do not wait for laboratory confirmation.**

Blood samples should be drawn to measure plasma pseudocholinesteraseand red blood cell AChE levels. Depressions of plasma pseudocholinesteraseand/or RBC acetylcholinersterase enzyme activities are generally available biochemical indicators of excessive organophosphate absorption. Certain organo-phosphates may selectively inhibit either plasma pseudocholinesterase or RBC acetylcholinesterase.22 A minimum amount of organophosphate must be absorbed to depress blood cholinesterase activities, but enzyme activities, especially plasma pseudocholinesterase, may be lowered by dosages considerably less than are required to cause symptomatic poisoning. The enzyme depression is usually

apparent within a few minutes or hours of significant absorption of organophosphate. Depression of the plasma enzyme generally persists several days to a few weeks. The RBC enzyme activity may not reach its minimum for several days, and usually remains depressed longer, sometimes 1-3 months, until new enzyme replaces that inactivated by organophosphate. The below table no. 2lists approximate lower limits of normal plasma and RBC cholinesterase activities of human blood, measured by several methods [10]

Table 2: lower limits of normal plasma and red cell cholinesterase activity in humans

APPROXIMATE LOWER LIMITS OF NORMAL PLASMA AND RED CELL CHOLINESTERASE ACTIVITIES IN HUMANS*

Methods	Plasma	RBC	Blood	Whole units
pH (Michel)	0.45	0.55		ΔpH per mL per hr
pH Stat (Nabb-Whitfield)	2.3	8.0		μM per mL per min
BMC Reagent Set (Ellman-Boehringer)	1,875		3,000	mU per mL per min
Dupont ACA	<8			Units per mL
Garry-Routh (Micro)			Male 7.8 Female 5.8	μM-SH per 3mL per min
Technicon	2.0	8.0		μM per mL per min

* Because measurement technique varies among laboratories, more accurate estimates of minimum normal values are usually provided by individual laboratories.

TREATMENT

1. Airway protection: Ensure that a clear airway exists. Intubate the patientand aspirate the secretions with a large-bore suction device if necessary.Administer oxygen by mechanically assisted pulmonary ventilation if respiration is depressed. **Improve tissue oxygenation as much as possible beforeadministering atropine, so as to minimize the risk of ventricularfibrillation.** In severe poisonings, it may be necessary to support pulmonaryventilation mechanically for several days.

2. Atropine sulphate: Administer atropine sulfateintravenously, or intramuscularlyif intravenous injection is not possible. Remember that atropine can beadministered through an endotracheal tube if initial IV access is difficult toobtain. Depending on the severity of poisoning, doses of atropine ranging fromvery low to as high as 300 mg per day may be

required. The objective of atropine antidotal therapy is to antagonize the effects ofexcessive concentrations of acetylcholine at end-organs having muscarinic receptors.Atropine does not reactivate the cholinesterase enzyme or acceleratedisposition of organophosphate. Recrudescence of poisoning may occur if tissueconcentrations of organophosphate remain high when the effect of atropinewears off. Atropine is effective against muscarinic manifestations, but it isineffective against nicotinic actions, specifically muscle weakness and twitching, and respiratory depression.

3. Glycopyrolate: It has been studied as an alternative to atropine and found tohave similar outcomes using continuous infusion. Ampules of 7.5 mg ofglycopyrolate were added to 200 mL of saline and this infusion was titrated to thedesired effects of dry mucous membranes and heart rate above 60 beats/min.During this study, atropine was used as a bolus for a heart rate less than 60 beats/min. The other apparent advantage to this regimen was a decreased number ofrespiratory infections. This may represent an alternative when there is a concernfor respiratory infection due to excessive and difficult to control secretions, and inthe presence of altered level of consciousness where the distinction betweenatropine toxicity or relapse of organophosphate poisoning is unclear.

4. Pralidoxime: Before administration of pralidoxime, draw a blood sample(heparinized) for cholinesterase analysis (since pralidoxime tends to reverse thecholinesterase depression). Administer pralidoxime (Protopam, 2-PAM) a cholinesterasereactivator, in cases of severe poisoning by organophosphate pesticidesin which respiratory depression, muscle weakness, and/or twitching aresevere. When administered early (usually lessthan 48 hours after poisoning), pralidoxime relieves the nicotinic as well as themuscarinic effects of poisoning. Pralidoxime works by reactivating the cholinesteraseand also by slowing the “aging” process of phosphorylated cholinesteraseto a non-reactivatable form.

5. Skin decontamination: In patients who have been poisoned by organophosphatecontamination of skin, clothing, hair, and/or eyes, decontaminationmust proceed concurrently with whatever resuscitative and antidotal measuresare necessary to preserve life. Flush the chemical from the eyes with copiousamounts of clean water. If no symptoms are evident in a patient who remainsalert and physically stable, a prompt shower and shampoo may be appropriate,provided the patient is carefully observed to insure against any sudden appearanceof poisoning. If there are any indications of weakness, ataxia, or otherneurologic impairment, clothing should be removed and a complete bath andshampoo

given while the victim is recumbent, using copious amounts of soapand water. Attendants should wear rubber gloves as vinyl provides no protectionagainst skin absorption. Surgical green soap is excellent for this purpose,but ordinary soap is about as good. Wash the chemical from skin folds and fromunder fingernails.

6. Gastrointestinal decontamination: If organophosphate has been ingestedin quantity probably sufficient to cause poisoning, consideration should be givento gastrointestinal decontamination, as outlined in Chapter 2, General Principles.If the patient has already vomited, which is most likely in serious exposures,further efforts at GI decontamination may not be indicated. In significantingestions, diarrhea and/or vomiting are so constant that charcoal adsorptionand catharsis are not indicated.

7. Observation: Observe patient closely for at least 72 hours to ensure thatsymptoms (sweating, visual disturbances, vomiting, diarrhea, chest and abdominaldistress, and sometimes pulmonary edema) do not recur as atropinization iswithdrawn. In very severe poisonings by ingested organophosphates, particularlythe more lipophilic and slowly hydrolyzed compounds, metabolic dispositionof toxicant may require as many as 5-14 days. In some cases, this slowelimination may combine with profound cholinesterase inhibition to requireatropinization for several days or even weeks. As dosage is reduced, the lungbases should be checked frequently for crackles. If crackles are heard, or if thereis a return of miosis, bradycardia, sweating, or other cholinergic signs, atropinisation must be re-established promptly.

8. Furosemide: Itmay be considered if pulmonary edema persists in the lungseven after full atropinization. It should not be used until the maximum benefit ofatropine has been realized. Consult package insert for dosage and administration.

9. Pulmonary ventilation: Particularly in poisonings by large ingested dosesof organophosphate, monitor pulmonary ventilation carefully, even after recoveryfrom muscarinic symptomatology, to forestall respiratory failure. In somecases, respiratory failure has developed several days following organophosphateingestion, and has persisted for days to weeks.

10. Hydrocarbon aspiration: may complicate poisonings that involve ingestionof liquid concentrates of organophosphate pesticides. Pulmonary edemaand poor oxygenation in these cases will not respond to atropine and should betreated as a case of acute respiratory distress syndrome.

11. Cardiopulmonary monitoring: In severely poisoned patients, monitorcardiac status by continuous ECG recording. Some organophosphates have significantcardiac toxicity.

12. Seizure control: Rarely, in severe organophosphate poisonings, convulsionsoccur despite therapy with atropine and pralidoxime. Insure that causesunrelated to pesticide toxicity are not responsible: head trauma, cerebral anoxia,or mixed poisoning. Drugs useful in controlling convulsions are benzodiazepines (diazepam or lorazepam).

13. Contraindications: The following drugs are contraindicated in nearly allorganophosphate poisoning cases: morphine, succinylcholine, theophylline,phenothiazines, and reserpine. Adrenergic amines should be given only if thereis a specific indication, such as marked hypotension.

14. Re-exposures: Persons who have been clinically poisoned by organophosphatepesticides should not be re-exposed to cholinesterase-inhibitingchemicals until symptoms and signs have resolved completely and blood cholinesteraseactivities have returned to at least 80 percent of pre-poisoning levels.If blood cholinesterase was not measured prior to poisoning, blood enzymeactivities should reach at least minimum normal levels before the patient is returned to a pesticide-contaminated environment.

15. Do not administer atropine or pralidoxime prophylactically to workersexposed to organophosphate pesticides. Prophylactic dosage with either atropineor pralidoxime may mask early signs and symptoms of organophosphate poisoningand thus allow the worker to continue exposure and possibly progress tomore severe poisoning. Atropine itself may enhance the health hazards of theagricultural work setting: impaired heat loss due to reduced sweating and impairedability to operate mechanical equipment due to blurred vision.This can be caused by mydriasis, one of the effects of atropine [11-16]

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CONFLICT OF INTEREST

There is no conflict of interest of any of the authors of this article

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