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# Current review on organophosphorus poisoning

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## ABSTRACT

*Organophosphorus (OP) compounds constitute a heterogeneous category of chemicals specifically designed for the control of pests, weeds or plant diseases. Our review article mainly focused on OP poisoning, especially with pesticides, its severity and management of toxic exposure. We developed a search strategy to find publications about OP poisoning and its management. So, we searched Science Direct, Medline and PubMed bibliographic databases using the key phrases causes of organophosphorus compounds, diagnosis, management of OP poisoning and drugs under clinical trials. Our review article examines pathophysiology, clinical manifestations, toxicokinetics of OP poison, its prevention and management. In addition to that, our review suggested antioxidants should be administered for OP poisoning patients to reduce severity. We conclude that in future, the ministry of agriculture of developing countries especially India, should concentrate on the optimization and monitoring of usage of OP compounds as pesticides and furthermore, encouraging the farmers to use natural pesticides rather than chemical pesticides.*

**Key words:** Antioxidants, atropine, organophosphorus poisoning, pralidoxime, therapy.

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## INTRODUCTION

Organophosphorus (OP) compounds have been widely used for a few decades in agriculture for crop protection and pest control, thousands of these compounds have been screened and over one hundred of them have been marketed for these purposes [1]. OPs constitute a heterogeneous category of chemicals specifically designed for the control of pests, weeds or plant diseases. Their application is still the most effective and accepted means for the protection of plants from pests, and has contributed significantly to enhanced agricultural productivity and crop yields [2]. Some have also been used in the medical treatment of myasthenia gravis, e.g. diisopropyl phosphorofluoridate (DFP) [3], tetraethyl pyrophosphate (TEPP) [4], and octomethyl pyrophosphotetramide (OMPA) [5]. Some OP esters are still used to treat glaucoma (Ecothiopate). In addition to these beneficial agricultural, veterinary, and medical uses, some highly potent OP anticholinesterase compounds, including tabun, sarin, soman, and VX have

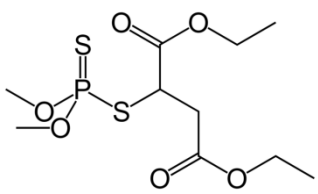
been used as “nerve gases” in chemical warfare. They are also been used as plasticizers, stabilizers in lubricating and hydraulic oils, flame retardants, and gasoline additives [6].

A total of about 890 active ingredients are registered as pesticides in USA and currently marketed in some 20,700 pesticide products. U.S pesticide expenditures totalled more than $11 billion in 2000 and 2001 [7]. Many of these compounds, because of their environmental persistence, will linger in our environment for many years to come. All people are inevitably exposed to pesticides, through environmental contamination or occupational use. The general population is exposed to the residues of pesticides, including physical and biological degradation products in air, water and food. Occupational exposure occurring at all stages of pesticide formulation, manufacture and application involves exposure to complex mixtures of different types of chemicals, active ingredients and by-products present in technical formulations such as impurities, solvents and other compounds produced during the storage procedure. Moreover, although inert ingredients have no pesticidal activity, they may be biologically active and sometimes the most toxic component of a pesticide formulation. Pesticides act selectively against certain organisms without adversely affecting others. Absolute selectivity, however, is difficult to achieve and most pesticides are a toxic risk also to humans [2]. The common use of insecticides in public health and agricultural schedules has caused severe environmental pollution and potential health hazards including severe acute and chronic cases of human and animal poisonings.[8] So we developed a search strategy to find publications about OP poisoning and its management in Science Direct, Medline and PubMed bibliographic databases using the key phrases causes of organophosphorus compounds, diagnosis, management of OP poisoning and drugs under clinical trials.

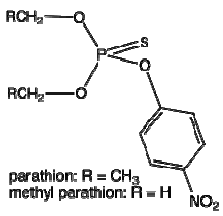
**EPIDEMIOLOGY:**

**Figure: I Chemical structures of some OP compounds.**

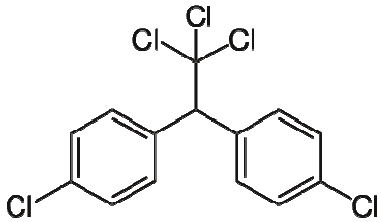
**Malathion**



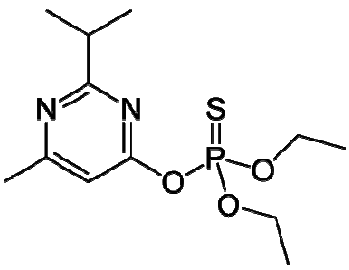
**Parathion**



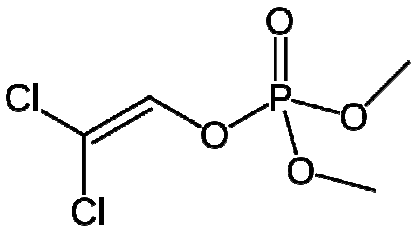

**DDT**



**Diazinon**



**Dichlorvos**



**Global Status:**

The organophosphate compounds are most commonly associated with serious human toxicity, accounting for more than 80% of pesticide-related hospitalizations [9]. In contrast to the past, when chlorinated hydrocarbon compounds such as DDT were commonly used, organophosphate

insecticides have become increasingly popular for both agricultural and home use because their unstable chemical structure leads to rapid hydrolysis and little long-term accumulation in the environment [10]. Chemical structures of some OP compounds are shown in Figure I.

This widespread use, however, has resulted in increased numbers of human poisonings. Through the 1970s, the Environmental Protection Agency estimated that 3,000 hospitalizations per year were required for insecticide poisoning in the United States, with a fatality rate of 50% in the paediatric age group and 10% in adults [11, 12]. In 1983 data from the American Association of Poison Control Centres indicated that the national incidence of insecticide exposures was 77,000, of which 33,000 involved organophosphates [13]. The continued use of such chemicals will likely increase these statistics in the future.

The first global estimates of the extent of pesticide poisoning were published in 1990 by the World Health Organisation [14]. Based on extrapolations from limited data, it was estimated that 3 million cases of pesticide poisonings occurred world-wide annually with 220,000 deaths, the majority intentional. The WHO estimates, based on 2001 data, that 849,000 people die globally from self-harm each year [15]. How many of these cases are a result of poisoning with pesticides is not known. However, poisoning is the commonest form of fatal self-harm in rural Asia, accounting for over 60% of all deaths [16, 17, 18], and is of far greater importance than hanging, and other physical forms of self-harm. Furthermore, a review of poisoning studies reveals that pesticides are the commonest means of self-poisoning in many rural areas and associated with a high mortality rate [19]. A recent national survey in Bangladesh showed that 14% of all deaths (3971 of 28,998) of women between 10 and 50 years of age were due to self-poisoning, the majority with pesticides [20]. The problem is particularly severe in Sri Lanka [21] where pesticide poisoning was the commonest cause of hospital death in six rural districts during 1995 [22]. In many countries, the widespread availability of acutely toxic pesticides used in agriculture has made selection of pesticides as the agents of choice for self-harm well known to both health care workers and public health authorities [23, 24, 25].

**National status:**

The importance of pesticides in India can be understood from the fact that agriculture is a major component of the Indian economy: It contributes 22% of the nation's GDP and is the livelihood of nearly 70% the country's workforce. Globally, due to consolidation in the agrochemical industry, the top five multinational companies control almost 60% of the market. In India, the industry is very fragmented, with about 30 to 40 large manufacturers and about 400 formulators. The use pattern is skewed towards insecticides, which accounted for 67% of the total pesticide consumption in 2006. The potential adverse impact on human health from exposure to pesticides is likely to be higher in countries like India due to easy availability of highly hazardous products, and low risk awareness, especially among children and women. Overexposure to pesticides can occur before spraying– because of easy access for children, lack of adequate labelling and during mixing – during spraying and after spraying operations. Spray operators and bystanders can be affected. Having cheap and easily available highly hazardous pesticides at hand increases the incidence of intentional pesticide poisonings [26]. The effective number of cases of pesticide poisoning occurring in India annually has been estimated by G. Ravi et al 2007 to be up to 76 000, much higher than the figure of NCRB. Furthermore, Gunell et al, 2007 calculate that the number of intentional cases alone reaches some 126,000 cases annually [27].

**Pathophysiology:**

Organophosphate compounds avidly bind to cholinesterase molecules and share a similar chemical structure. In human beings, the two principal cholinesterases are RBC, or true

cholinesterase (acetylcholinesterase), and serum cholinesterase (pseudocholinesterase) [9]. Normally the cholinesterases rapidly hydrolyze the neurotransmitter acetylcholine into inactive fragments of choline and acetic acid after the completion of neurochemical transmission. The neurotransmitter acetylcholine is present in the terminal endings of all postganglionic parasympathetic nerves, at myoneural junctions, and at both parasympathetic and sympathetic ganglia. The major toxicity of organophosphate compounds is the covalent binding of phosphate radicals to the active sites of the cholinesterases, transforming them into enzymatically inert proteins [9, 10]. Organophosphates thus act as irreversible cholinesterase inhibitors because the organophosphate-cholinesterase bond is not spontaneously reversible without pharmacological intervention. The inhibition of cholinesterase activity leads to the accumulation of acetylcholine at synapses, causing overstimulation and subsequent disruption of transmission in both the central and peripheral nervous systems. Exposure to organophosphate compounds will, therefore, interfere with synaptic transmission peripherally at muscarinic neuroeffector junctions and nicotinic receptors within sympathetic ganglia and at skeletal myoneural junctions. This is accomplished by an overstimulation of acetylcholine receptor sites that leads to a variety of physiologic and metabolic derangements. Disruption of transmission also will occur at the acetylcholine receptor sites within the central nervous system [10].

**Toxicokinetics of OPS:**
Limited human toxicokinetic data are available and those aspects which are clinically important will be stressed.

**Absorption:** The degree of absorption depends on the contact time with the skin, the lipophilicity of the agent involved and the presence of solvents, for example xylene, and emulsifiers in the formulation which can facilitate absorption. For powders, the finer the powder the more rapid and complete is skin absorption. Other important factors include volatility of the pesticide (e.g. dichlorvos is much more volatile than Malathion), the permeability of clothing, the extent of coverage of the body surface and personal hygiene. The rate of absorption also varies with the skin region affected. For example, parathion is absorbed more readily through scrotal skin, axillae and skin of the head and neck than it is through the skin of the hands and arms. It is probable that traumatized skin or the presence of dermatitis allows greater absorption of OP compounds. In one study, the mean amount of liquid parathion absorbed dermally was only 1.23% of the measured potential dermal exposure [28, 29].

**Distribution and Storage:** Following absorption, OP compounds accumulate rapidly in fat, liver, kidneys and salivary glands. The phosphorothioates (P=S), for example diazonin, parathion, and bromophos, are more lipophilic than phosphates (P=O), for example dichlorvos, and are therefore stored extensively in fat which may account for the prolonged intoxication and clinical relapse after apparent recovery which has been observed in poisoning from these OP insecticides. OP compounds generally are lipophilic and therefore cross the blood / brain barrier in most cases [28].

**Biotransformation:** Phosphates (P=O) are biologically active as acetylcholinesterase (AChE) inhibitors, whereas phosphorothioates (P=S) need bioactivation to their phosphate analogues (oxon) to become biologically active. As a consequence, the features of intoxication after exposure to phosphorothioates (P=S) are delayed unless aerial oxidation has occurred already to generate traces of oxon. OP compounds other than phosphates (P=O) are metabolically activated to their corresponding oxon by oxidation desulfuration mediated by P450 isoforms, by flavin-containing mono-oxygenase enzymes, by N-oxidation and by S-oxidation. The oxons which

inhibit AChE can be deactivated by hydrolases, such as the carboxylases and by A-esterases, for example paraoxonase [28, 30].

**Elimination:** Elimination of metabolites occurs mostly in urine with lesser amounts in faeces and expired air. Some OPs, for example dichlorvos which is not stored in fat to any great extent, may be eliminated in hours whereas the inhibitory oxon of chlorpyrifos or dementon-S-methyl may persist for days because of their extensive storage in fat [28].

**BIOCHEMICAL CHANGES:**

Organophosphorus compounds have many toxicological effects on the body, some are discussed here:

**Respiratory disorders:** OPs caused a central failure of breathing in all animals. The key findings were rapidly progressive bradypnoea leading to apnoea due to loss of respiratory effect. Loss of central inspiratory drive due to poisoning has been found [31]. The lack of paralysis of respiratory muscles is also supported by other studies that demonstrated intact diaphragmatic following OP poisoning [32].

**Hepatological disorders:** Liver is the organ where activation and detoxification of OP compounds takes place. But they are eliminated primarily through kidneys [33]. Earlier the profile of liver marker enzymes, antioxidant enzymes and essential trace elements were found to be adversely affected after OP intoxication to rats [34]. The histopathological changes observed in human liver observed in a forensic laboratory are: Congestion, Centrilobular necrosis, Fatty changes, Alcoholic hepatitis and Sinusoidal dilatation [35]. At high doses of OP, rats exhibited extreme injury in their liver [36].

**Cardiovascular disorders:** Povoa et al have reported that OPs induced acute poisoning with myocardial necrosis [37]. Saadeh et al, reported that there will be an increased in Creatinine kinase and lactate dehydrogenase levels, after OP poisoning [38]. Cardiac Manifestations: Sinus tachycardia, sinus bradycardia, hypertension, hypotension, impaired heart rate and force contraction [39]. ECG changes: Prolonged QTc interval, ST segment elevation, low amplitude T waves, extrasystole and prolonged PR interval [40].

**Neurological disorders:** Neuronal necrosis has been observed in multiple cortical and subcortical regions in experimental rats exposed to large acute doses of OP compounds [41, 42].

OP also leads to a delay in stimulus classification, which in turn depends on attentional resources and the working memory system of the brain, this impairment appears to persist even 6 months after poisoning [43]. Several chronic CNS disturbances due to acute or chronic OP agent poisoning have been reported in isolated cases or in worker cohorts. The syndromes vary widely and include parkinsonian and pseudobulbar signs, alterations in effect, libido and memory, psychiatric or more insidious neuropsychological dysfunction and a cerebellar syndrome [6].

**Hormonal imbalance:** In late 20th century, several experimental and epidemiological studies regarding hormonal imbalance especially sex hormones leading to adverse developmental outcomes related to pesticide exposure, including foetal death, intrauterine growth restriction, congenital malformations and male / female fertility have been published [44]. Living in rural areas where large amounts of pesticides are applied represents a risk factor for fertility [45].

**Oesophageal effects:** Emergent esophago-gastroscopy revealed circumferential hyperthermia, oedema and bleeding throughout esophagus [46].

**Renal impairment:** Many studies reviewed by the Ontario College show positive associations between solid tumours and pesticide exposure, including kidney cancer. Children are constantly exposed to low levels of pesticides in their food and environment, an elevated risk of kidney cancer was associated with paternal pesticide exposure through agriculture. It has also been reported that the chronic exposure to pesticides leads to kidney failure [47].

**Oxidative stress and Antioxidant status:** Studies have shown that OP poisoning is associated with enhanced lipid peroxidation, reduced Glutathione levels and elevated antioxidant status and increased oxidative stress [48, 49].

**CLINICAL MANIFESTATIONS:**

Classification of signs and symptoms of acute organophosphate poisoning according to receptor site and type is given in the Table I [50].

**Table: I Clinical Manifestations of OP poisoning according to receptor type**

| Muscarinic | Nicotinic | Central |
|---|---|---|
| Miosis | Muscle Fasciculations | Unconsciousness |
| Blurred vision | Paralysis | Confusion |
| Nausea | Pallor | Toxic psychosis |
| Vomiting | Muscle weakness | Seizures |
| Diarrhoea | Hypertension | Fatigue |
| Salivation | Tachycardia | Respiratory Depression |
| Lacrimation | Mydriasis (rare) | Dysarthria |
| Bradycardia | | Ataxia |
| Abdominal pain | | Anxiety |
| Diaphoresis | | |
| Wheezing | | |
| Urinary Incontinence | | |
| Fecal Incontinence | | |

**Diagnosis:**

Diagnosis of OP poisoning is based on characteristic clinical features, (miosis is considered to be a very strong indicator of organophosphate poisoning) and history of exposure to a known OP compound. Estimation of serum or RBC cholinesterase level and electrodiagnostic tests is helpful in confirming the diagnosis. Clinical features of OP poisoning appear when RBC cholinesterase activity is <75% of normal and in clinical overt poisoning it is usually <10%. In general, however, serial studies have failed to document a strict relationship between the severity of clinical manifestations and prognosis [50, 51, 52].

**Laboratory Findings:** Routine laboratory studies typically are unremarkable, with several notable exceptions. Non-ketotic hyperglycaemia and glycosuria have been observed in numerous case reports. Hypokalemia also has been noted occasionally. Leukocytosis, both with and without a left shift, was a common finding in Hayes's study [53]. Elevated serum amylase secondary to pancreatic injury because of parasympathetic overstimulation and hypersecretion has been noted in human beings. The ECG may display a variety of abnormalities in acute organophosphate poisoning like, sinus bradycardia, atrioventricular block, and ST&T wave abnormalities and prolongation of the Q-T interval also has been commonly observed [50]. Incidence of laboratory features in acute OP poisoning in humans has been shown in Table II.

**Table: II Laboratory features observed by Hayes *et al*.**

| Laboratory investigations | Percentage of patients (Hayes et al, 1978) |
|---|---|
| Serum cholinesterase (markedly depleted) | 97 |
| Neutrophil leukocytosis | 46 |
| Proteinuria | 19 |
| Glycosuria | 14 |
| Hyperglycemia | 7 |
| Abnormal ECG (excluding bradycardia/tachycardia) | 5 |

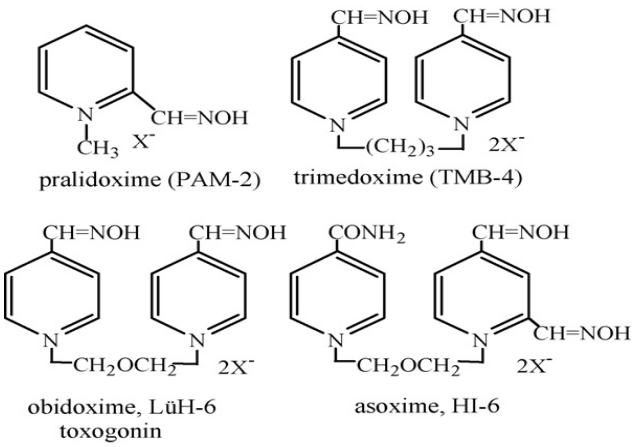
**Management:**

**Initial phase:** Severe acute OP poisoning is a medical emergency. Treatment must ensure that the patient has a patent airway and adequate breathing and circulation. Ideally, oxygen should be provided at the first priority. The patient should be placed in the left lateral position, with the neck extended. This position reduces risk of aspiration; helps keep the airway patent, and could decrease pyloric emptying and absorption of poison. Supportive care should include giving fluids and control of blood glucose [54].

**Maintenance phase:**
Muscarinic antagonist drugs: Although atropine remains the mainstay of therapy worldwide, other muscarinic antagonists have been studied in animals. The main adverse effect of atropine is anticholinergic delirium in patients who receive too high doses. Hyoscine was used successfully to treat a patient with severe extra-pyramidal features but few peripheral signs. Atropine will probably remain the antimuscarinic agent of choice until high-quality randomized trials show another muscarinic antagonist to have a better benefit-to-harm ratio because it is available widely, affordable and moderately able to penetrate into the CNS. No known randomized controlled trials have compared different regimens of atropine for either loading or continuation therapy. The aim of early therapy is to reverse cholinergic features and to improve cardiac and respiratory function as quickly as possible.[55]

According to IPCS (1989) an initial trial dose of atropine, 1–2mg (0.05 mg/kg) intravenously, should be given slowly over 3min, and then repeated every 5–10 min if there is no observable adverse effect.[56] In symptomatic children, intravenous dose of 0.015–0.05 mg/kg atropine should be administered every 15 min as needed. Atropine may then be repeated or increased in increments at 15–30 min intervals until bronchosecretion is cleared and the patient is atropinized (dilated pupils, dry skin, and skin flushing) which should be maintained during further treatment. Repeated evaluations of the quantity of the secretions through regular auscultation of the lungs are the only adequate measure of atropinization in the severely poisoned patient. The dose may be increased as required [57].

**Oximes:** Oximes reactivate acetylcholinesterase inhibition by Organophosphorus. Among the many classes of oximes investigated so far, those with clinical application can be divided in two groups – the monopyridinium and bispyridinium oximes. Currently, the only used monopyridinium oxime is pralidoxime (PAM-2), while the most significant bispyridinium oximes comprise: trimedoxime (TMB-4), obidoxime (LuH-6, Toxogonin) and asoxime (HI-6), and their chemical structure is presented in Figure II. There is still no international consensus on the choice of most effective oxime and on dosing regimen.
Figure: II Structures of some Oximes.




Pralidoxime was discovered in the mid-1950s by Wilson and colleagues, and was soon successfully introduced into clinical practice for patients with parathion poisoning. Other oximes, such as obidoxime and trimedoxime, have been developed but Pralidoxime remains the most widely used. It has four salts: chloride, iodide, metisulfate and mesilate. The chloride and iodide salts are used widely, but metisulfate and mesilate are used mostly in France, Belgium and the UK. The chloride salt has advantages over iodide – in particular its smaller molecular weight (173 vs. 264), which provides 1-5 times more active compound per gram of salt than does iodide. A high dose of Pralidoxime iodide also puts patients at risk of thyroid toxicity, especially if given for a long period [58].

Despite the beneficial effects of Pralidoxime first noted with parathion poisoning, its effectiveness has been much debated, with many Asian clinicians unconvinced of its benefit. In particular, two randomized controlled trials in Vellore, India in the early 1990s noted that low-dose infusions of Pralidoxime may cause harm. The absence of clinical benefit could relate to trial design (suboptimum dose, or bias in allocation). Alternatively, this result could suggest that Pralidoxime is ineffective in their patients, perhaps because of the specific pesticide ingested, the amount ingested or the patient's long delay before Pralidoxime is given. Observational studies of Pralidoxime and obidoxime suggest that the ability to reverse acetylcholinesterase inhibition with oximes varies with the pesticide ingested [59].

The clinical effects can also be limited by high concentrations of OP in the blood after ingestion of a large dose – the pesticide simply re-inhibits any acetylcholinesterase that the oximes reactivate. Oximes will also not be effective for improvement of outcomes if the patient develops severe complications such as aspiration pneumonia or hypoxic brain injury before treatment. Such complications take place most often with fast-acting pesticides such as parathion and dichlorvos [55].

WHO recommends that oxime is given to all symptomatic patients who need atropine [60]. To ensure a therapeutic concentration, a loading dose of Pralidoxime chloride or obidoxime is given, then a continuous infusion. The loading dose of oxime should not be given rapidly as a bolus because this method causes vomiting (risking aspiration), tachycardia and diastolic hypertension [61].

In poisoning with OP pesticides pralidoxime chloride should be administered to adults in a dose of 500 mg/h, continuously maintained until clinical improvement is obtained, or 30 mg/kg body weight bolus intravenously over 4–6 h or 8–10 mg/kg/h intravenously until full recovery occurs. In children, Pralidoxime chloride should be administered in a dose of 25 mg/kg intravenously for

15–30 min, followed by a continuous infusion of 10–20 mg/kg/h. The therapy can continue for 18 h or longer, depending on the clinical status [56].

Obidoxime when administered to human volunteers by intramuscular route obidoxime 5 mg/kg produced a plasma concentration >4 mg/L, from 5min after injection to 3 h. Adverse effects of obidoxime in male volunteers were described as pallor, nausea, burning sensation, headache, generalized weakness, sore throat, and paresthesia of the face. Following high doses of obidoxime (several grams per day) in severely OP poisoned patients, hepatotoxic effects were occasionally observed including increased serum transaminases, jaundice and cholestasis [57].

Obidoxime should be administered in adults at dose of 250mg given by slow intravenous injection followed by continuous infusion of 750 mg/24 h (0.4 mg/kg/h) to reach plasma concentrations of 10–20 µmol/L. Intramuscular dosing is possible when the intravenous route is inaccessible. In children, the dose of obidoxime is 3–6 mg/kg slowly administered intravenously over at least 5min [56].

Asoxime (HI-6): Clinical studies showed that HI-6 dosed at either 250mg or 500mg by intramuscular route reached plasma concentrations >4 mg/L in 4–6 min. This concentration was maintained for 125 min following the lower dose (250 mg) and 200 min following the higher dose (500 mg). They have administered HI-6 four times a day as a single intramuscular injection of 500mg with atropine and diazepam treatment. Oxime therapy was started on admission and continued for 2–7 days.

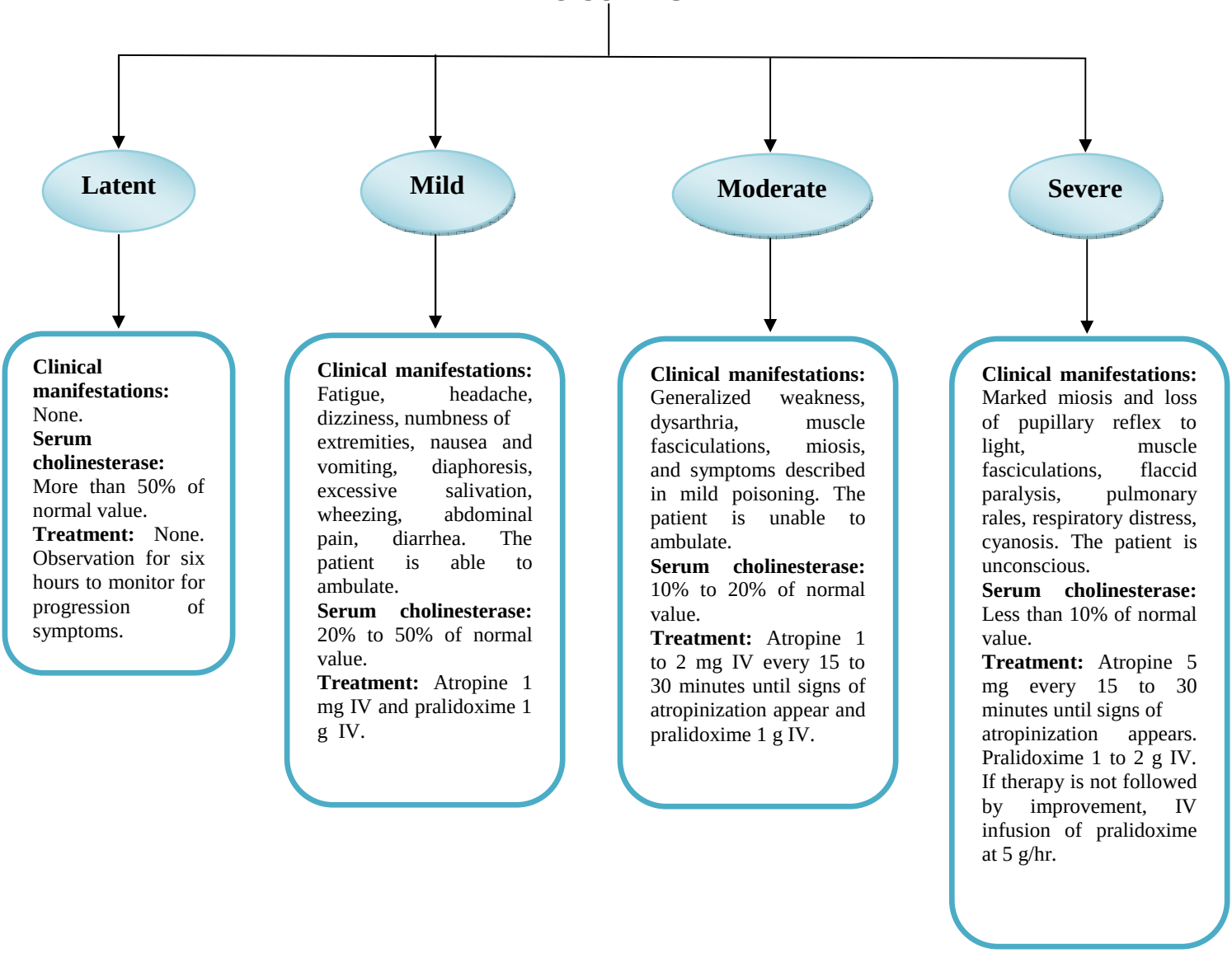
A clinical study performed on 22 healthy human volunteers did not reveal any adverse effects when HI-6 was given in doses up to 500mg by oral route. HI-6 is considered to be a very promising bispyridinium oxime in medical treatment following exposure to most nerve agents. A disadvantage of HI-6 compared to other available oximes is its lack of stability in aqueous solutions. HI-6 was considered to be an effective antidote (in combination with atropine and diazepam) in treatment of patients poisoned with OP insecticides [57].

It is important to note that oximes are not effective for improvement of outcomes if the patient develops severe complications such as aspiration pneumonia or hypoxic brain injury before treatment. Such complications take place with fast-acting pesticides such as parathion and dichlorvos [59].

**Benzodiazepines:** Patients poisoned with OP frequently develop agitated delirium. The cause is complex, with contributions from the pesticide itself, atropine toxicity, hypoxia, alcohol ingested with the poison and medical complications. Although the mainstay of management is prevention or treatment of underlying causes, some patients need pharmacotherapy. Acutely agitated patients will benefit from treatment with diazepam [55].

Diazepam is first-line therapy for seizures are uncommon in well oxygenated patients with OP poisoning. Seizures seem to be more common with OP nerve agents (such as soman and tabun). Animal studies suggest that diazepam reduces neural damage and prevents respiratory failure and death, but studies in humans are few [62]. In addition, the classification and treatment of OP poisoning has been shown in Figure: III.

**Figure: III Classification & treatment of OP poisoning.**




**Gastrointestinal decontamination:** Gastric lavage is often the first intervention poisoned patients receive on presentation to hospital, sometimes at the expense of resuscitation and giving antidote. No evidence shows any form of gastric decontamination to benefit patients poisoned with OP. gastric decontamination should only be done after the patient has been stabilized and treated with oxygen, atropine and an oxime.

Gastric lavage is the most common form of decontamination for OP poisoning despite the absence of randomized controlled trials to confirm benefit. The rate of absorption of OP from human bowel is not known; however, with some pesticides, the rapid onset of poisoning in animals and humans suggests that absorption is rapid, occurring within minutes of ingestion. The time window for effective lavage is therefore probably short. Guidelines for treatment of drug self-poisoning suggest that the lavage should be considered only if the patient arrives within 1 hour of ingesting poison.

Repeated gastric lavages are recommended in China to remove pesticide remaining in the stomach, although substantial amounts of OP are unlikely to remain in the stomach after one

lavage. Ipecacuanha-induced emesis should not be used in OP poisoning. Patients poisoned with OP can rapidly become unconscious, risking aspiration if ipecacuanha has been given.

Charcoal might be given too late, or the solvent might interfere with binding. No evidence suggests that patients with pesticide poisoning benefit from treatment with activated charcoal [55, 63].

**Other therapies:** Current therapy works through only few mechanisms. Several new therapies have been studied but results were inconclusive. However, future research might reveal several affordable therapies working at separate sites that could complement present treatments.

 Magnesium sulphate blocks ligand-gated calcium channels, resulting in reduced acetylcholine release from pre-synaptic terminals, thus improving function at neuromuscular junctions, and reduced CNS over-stimulation mediated via NMDA receptor activation.

 Sodium bicarbonate is sometimes used for treatment of OP poisoning in Brazil and Iran, in place of oximes. Increases in blood pH (up to 7.45 – 7.55) have been reported to improve outcome in dogs through an unknown mechanism [64].

 The alpha2-adrenergic receptor agonist clonidine also reduces acetylcholine synthesis and release from presynaptic terminals. Animal studies show benefit of clonidine treatment, especially in combination with atropine, but effects in human beings are unknown.

 Removing OP from the blood could allow optimum action of other therapies. The roles of haemodialysis and haemofiltration are not yet clear; however, a recent non-randomized controlled study in China suggested a benefit of haemofiltration after poisoning with dichlorvos, which has poor solubility in fat and therefore should have a relatively small volume of distribution.

 Butyrylcholinesterase scavenges OP in plasma, reducing the amount available to inhibit acetylcholinesterase in synapses. It has been cloned and military research now aims to inject soldiers with the enzyme before exposure to OP nerve gases. Such a prophylactic approach is not practical for self-poisoning with OP because we cannot predict when a person is going to ingest the pesticide.

 A better approach than use of butylcholinesterase might be to give recombinant bacterial phosphotriesterases, or hydrolases. These proteins breakdown OP pesticides enzymatically and protect from poisoning. Future clinical development of such enzymes could reduce blood concentrations of OP, allowing optimum activity of other treatments [55].

**Final phase:** Patients are recovered in this phase. Further if required, drugs are prescribed based on their clinical manifestations.

**DRUGS FOR FUTURE:**

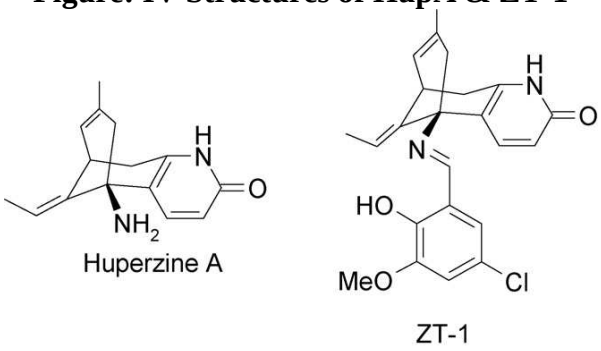
 **Huperzine A and ZT-1:**

HupA has been proven to be a powerful, highly specific, and reversible inhibitor of acetylcholinesterase (AChE. Shuangyiping, a tablet form of HupA produced from extracts of Huperzia serrata, was developed in 1996 (by one of the authors, Zhu) as a new drug for symptomatic treatment of Alzheimer's disease (AD) in China. HupA is also marketed in the

USA as a dietary supplement (as powdered Huperzia serrata in tablet or capsule form). Phase IV clinical trials in China have demonstrated that HupA significantly improves memory deficits in elderly people with benign senescent forgetfulness and in patients with AD or vascular dementia (VD), with minimal peripheral cholinergic side effects and no unexpected toxicity. HupA has better penetration through the blood–brain barrier, higher oral bioavailability, and longer duration of AChE inhibitory action.

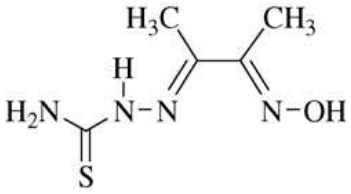
**ZT-1**: ZT-1 has similar properties to HupA regarding the ability to cross the blood–brain barrier, its oral bioavailability, and its longevity of action. ZT-1 is a promising new drug candidate and is expected to be the first Chinese new drug, with independent intellectual property rights owned by Chinese scientists, to move into the international major pharmaceutical markets [65]. The chemical structures of HupA and ZT-1 are given in Figure: IV.

**Figure: IV Structures of HupA & ZT-1**




**Butane - 2, 3-dionethiosemicarbazone** is an oxime with antioxidant properties. It has been demonstrated that butane-2,3-dionethiosemicarbazone has an antioxidant activity in scavenging different forms of reactive species (which are commonly generated in normal cellular oxygen metabolism playing some biological roles) like hydroxyl radicals, nitric oxide radicals, and hydrogen peroxide and as well as counteract its formation. It is also able to effectively counteract the lipid peroxidation induced by different oxidant agents. In ex vivo experiments it has been observed that the oxime depicted no significant change in glutathione levels. An in vitro study examined the capacity of this oxime to scavenge different forms of reactive species [66]. The structure of butane-2,3-dionethiosemicarbazone is given in Figure: V.

**Figure: V Structure of Butane – 2,3 – dionethiosemicarbazone.**




**Phosphotriesterases (PTEs):** The main enzymatic systems involved in the detoxification of OPs are phosphotriesterases, carboxylesterases, and glutathione-S-transferases. One of the main detoxification routes of OPs (both insecticides and nerve agents) is hydrolysis by esterases called ‘phosphotriesterases’ (PTEs). The products of the reaction display no phosphorylating capability, and therefore the hydrolysis of OPs by PTEs is considered a detoxification. PTEs are present throughout the phylogenetic scale (except in insects), from bacteria to mammals. The most intensively studied PTEs in mammals are human and rabbit serum paraoxonases [67].

**Public health issues and pests:**
Debilitating and deadly diseases that can be caused or spread by pests such as insects, rodents, and microbes pose a serious risk to public health. Examples of significant public health problems that are caused by pests include:

 Vector-Borne Diseases – Infectious diseases such as West Nile virus, Lyme disease, and rabies can be carried and spread by vector (disease-carrying) species such as mosquitoes, ticks, and rodents. Environmental Protection Agency (EPA) registers several pesticide products, including repellents that may be used to control the vectors that spread these diseases.

 Asthma and Allergies – Indoor household pests such as cockroaches can contribute to asthma and allergies. In addition to registering products to control these pests, EPA also provides information to the public about safely using these products in homes and schools.

 Microbial Contamination – Various microorganisms, including bacteria, viruses, and protozoa, can cause microbial contamination in hospitals, public health clinics, and food processing facilities. EPA registers antimicrobial products intended to control these microorganisms and help prevent the spread of numerous diseases.

 Avian Flu – Avian flu, sometimes called bird flu, is an infection that occurs naturally and chiefly in birds. Infections with these viruses can occur in humans, but the risk is generally low for most people. EPA works to register and make available antimicrobial pesticide products (sanitizers or disinfectants) that may be used to kill avian influenza virus on inanimate surfaces and to help prevent the spread of avian flu viruses. These products are typically used by the poultry industry to disinfect their facilities.

 Prions – Certain proteins found in cells of the central nervous system of humans and animals may exist in abnormal, infectious forms called “prions.” Prions share many characteristics of viruses, and may cause fatal diseases. In 2004, EPA determined that prions are considered to be a pest under FIFRA, and that products used to control prions are subject to EPA regulation.

 Anthrax –Biological agents such as Bacillus anthracis spores can cause a threat to public health and national security. EPA has issued emergency exemptions for several pesticides that were used in anthrax spore decontamination efforts, including (but not limited to): bleach, chlorine dioxide, ethylene oxide, hydrogen peroxide and peroxyacetic acid, methyl bromide, paraformaldehyde, and vaporized hydrogen peroxide.

**Prevention of OP Poisoning:**
Due to the toxicity of pesticides and the risk involved in treatments, there is general agreement that emphasis should be on preventing pesticide illness rather than relying on treatment.

 Ensure that there is always adequate ventilation when using or applying pesticides in the home or on pets, i.e. keep the doors and windows open at all times.

 Do not use pesticides indoors if they are only designed to be used outdoors.

 Always read and follow the pesticides label’s instructions and safety warnings at all times.

- Use ready-to-use products (i.e., no mixing needed) whenever possible.

- Remove all foodstuffs and water supplies in the home from the vicinity of pesticide application or alternatively keep them sufficiently covered.

- Wash all fresh fruit and vegetables adequately before consumption.

- Ensure that old pesticide or poison containers are safely discarded, instead of reusing them for storing or transporting drinking water. No matter how well you wash the container, it could still contain remnants of the pesticide.

- Do not transfer pesticides to other containers that children may mistake for cold drink or sweets container.

- Use gloves and other protective clothing when using or applying pesticides.

- Always wash your hands after using pesticides.

- Ensure regular washing of children's hands throughout the day.

- Ensure that all pesticides and poisons are stored out of reach of children and other unqualified persons i.e. locked in a poison store.

- Ensure adequate education of children with regard to poisons within the home environment.

- Never pour pesticides or household chemicals down the drain, into the toilet or storm water drains, rivers or dams [68].

**Role of antioxidants in op poisoning:** The toxicity of OP compounds is mediated by generation of nitric oxide and other free radicals. These toxic molecules can be counteracted by antioxidants such as vitamins C and E, spin traps, melatonin and low molecular weight thiols. The latter compounds can also increase the synthesis of glutathione, which can both ameliorate the OP-induced oxidative stress and enhance OP detoxification [64].

OP compounds are soluble in both water and lipid. Some OP compounds are highly soluble in water and can therefore easily contaminate aquatic ecosystems, thereby increasing the exposure risk of aquatic flora and fauna. Most of OP compounds are highly lipid – soluble agents and are well absorbed from the skin, oral mucous membranes, conjunctiva, gastrointestinal and respiratory tracts. Vitamin E is also a family of lipid – soluble vitamins, of which α-tocopherol is the most active form and is powerful biological antioxidant. Vitamin E may effectively minimize oxidative stress, lipid peroxidation and toxic effects of reactive oxygen species in biological systems. Selenium appears to function as an antimutagenic agent, preventing the malignant transformation of normal cells. These protective effects of selenium (as co-antioxidant) seem to be primarily associated with its presence in the seleno-enzymes, which are known to protect DNA and other cellular components from oxidative damage [69].

Hence, it is suggested to include antioxidants in the prescription of the patients with OP poisoning.

**Challenges:**

- Inadequate Forensic laboratories in Government hospitals.
- Inadequate Poison Information Centres.
- Inadequate knowledge in utilizing the pesticides.
- Lack of health professionals in toxicological studies.
- Lack of availability of newer antidotes.
- Easy availability of OP compounds (especially pesticides) in the market.
- Indeterminate quantitative estimation in patients.
- Elevation of respiratory failure.
- Raised diaphragmatic paralysis.
- High exposure/consumption of pesticides develops acute hemorrhagic pancreatitis.
- Utilization of pesticides increases health hazard in individuals leading to decrease in GDP.

All these challenges we can make full stop, if we ban OP compounds in commercial market.

## CONCLUSION

Organophosphorus compounds have become increasingly popular for agricultural, industrial and home use and represent a significant potential health risk. Our article reviewed the history, pathophysiology, clinical presentation, laboratory findings and management of toxic exposure to organophosphates. Prompt recognition and aggressive treatment of acute intoxication are essential in order to minimize the morbidity and mortality from these potentially lethal compounds. In future, the ministry of agriculture of developing countries especially India, should concentrate on the optimization and monitoring of usage of OP compounds as pesticides and furthermore encouraging the farmers to use natural pesticides rather than chemical pesticides.

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