Counter Measures in Organophosphorus Poisonings - A Review

Rakesh Bhragava[a], Ram Singh Chauhan[a]*, Lokendra Singh[a]
[a] Defence Research & Development Establishment, [a*]IDST Scientist Gwalior, India

Abstract

The ubiquitous organophosphates present a continuing health hazard for agriculture workers and as chemical warfare agents. The potential adverse impact on human health from exposure to pesticides is likely to be higher in India due to easy availability of these highly hazardous products, and low risk awareness, especially among children and women. Understanding manifestation of nerve agents' exposure through available data becomes useful for the treatment of organophosphate (OP) pesticides poisoning as well as developing strategy for the treatment of OP nerve agent, since pathophysiology of OP nerve agents and pesticides is qualitatively similar. This paper reviews the counter measures that are being followed as well as evolving ones in the case of poisoning due to OP compounds or nerve agents. Management consists of proper oxygenation, atropine in escalating doses and pralidoxime in high doses. Certain non-conventional drugs like Vitamin E & Vitamin C, Melatonin, Green tea extracts, Zinc Chloride, Ginger, Copper etc have been experimented with animal and experimental models. Each one of these gave certain positive response against OP compounds on these models.

KEYWORDS: Organophosphorus, Acetylcholinesterase, Atropine, Pralidoxime chloride, Oxidative stress

INTRODUCTION

Organophosphorus (OP) compounds are in use widely over decades in agriculture for crop protection and pest control. A pesticide is usually defined as a chemical substance, that is used against pests , insects, plant pathogens, weeds, mollusks, birds, mammals, fish, nematodes (roundworms) and microbes that compete with humans for food, have a propensity for spreading or are a vector for disease or simply a nuisance (Seabury *et al.*, 2013; Erdman, 2004).

In a country like India where agriculture is a major component of the economy and contributing about 22% of GDP, these compounds are easily available across the counter and known to be a house hold item for a family involved in agriculture. These compounds are highly toxic for crop-pests, insects as well as human. The easy accessibility of OP- products in the market has lead to significant increase for intentional poisoning for getting relived from family quarrels and/or financial burdens. As a result organophosphate (OP) poisoning has become a ubiquitous menace that has been associated with more than 200,000 deaths every year. According to an estimate the number of intentional cases alone reaches some 126,000 cases in 2007 alone in India (Ashish and Praveen, 2007). Deliberate self-poisoning has reached epidemic proportions in parts of the developing world where the toxicity of available poisons and sparse medical facilities ensure a high fatality rate (Reddy, 2006).

Organophosphorus compounds form a large family of about 50 000 chemical agents with properties that have important implications for man and military. They are also been used as plasticizers, stabilizers in lubricating and hydraulic oils, flame retardants, and gasoline additives. Some of these compounds were first synthesized in Germany in 1932. German chemist Willy Lange and his graduate student, Gerde von Krueger, first described the cholinergic nervous system effects of organophosphates, noting a choking sensation and a diminution of vision after exposure. This discovery later inspired the German chemist Gerhard Schrader in 1930s to experiment with these compounds as insecticide. From a series of these organophosphorus compounds, Tabun and Sarin were found to be very toxic to human, but of little use as pesticides because of their high volatility. Taking clue from high mammalian toxicity, these compounds were studied and developed as nerve agents for military purposes. Thus the development of nerve agents was a by-product of insecticide research and development (Reddy, 2006; Rodgers, 2006; Marrs *et al.*, 1996).

The military nerve agents are a family of highly toxic phosphoric acid esters, structurally related to the larger family of organophosphate compounds. Although compounds used as insecticide are less toxic than the nerve agents the toxicity of OP nerve agents and pesticides is qualitatively similar. The high toxicity of nerve agents arises from a carbon-phosphorous bond which is common to the nerve agents but is rare in the less-toxic organophosphate pesticides. However in general, treatment strategies are alike (Marrs *et al.*, 1996). Most organophosphates are highly lipid-soluble agents and are well absorbed from the skin, oral mucous membranes, conjunctiva and gastrointestinal and respiratory routes. The onset, severity and duration of poisoning is determined by the dose, route of exposure, physicochemical properties of the organophosphate (e.g. lipid solubility), rate of metabolism and whether the organophosphorylated-cholinesterase ages rapidly or otherwise (Karalliedde *et al.*, 2003; Moretto and Lotti, 2001).

There is a great deal of literature on nerve agents and organophosphate pesticides, including several books on chemical warfare agents (Vijayaraghavan *et al.*, 2010; Bajgar, 2004; Karalliedde *et al.*, 2001; Sidell *et al.*, 1997; Ballantyne and Marrs, 1992; Somani, 1992; Karczmar, 1970). However due to its topical importance continuous efforts are needed to upgrade the available knowledge. Understanding manifestation of nerve agents' exposure through available data becomes useful for the treatment of organophosphate pesticides poisoning as well, since toxicity of OP nerve agents and pesticides is qualitatively similar. This present paper reviews the counter measures that are needed in the case of positioning due to OP compounds or nerve agents poisoning.

Indian Scenario

Indian economy is still agriculture based. Organophosphorus (OP) compounds are used to protect against the pests, insects, plant pathogens in large quantity. During agricultural activities farmers are exposed to these chemicals and its implication on human health in India can be understood. Agriculture constitutes a livelihood of nearly 70% the country's workforce. The pesticide industry in India consists of about 30 to 40 large manufacturers and about 400 formulators and 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 India due to easy availability of these highly hazardous products, and low risk awareness, especially among children and women. Exposure to pesticides can also occur due to its easy access

for children, lack of adequate labeling and improper storing at home as well as during mixing and after spraying operations. Spray operators and bystanders can also be affected. Having cheap and easily available highly hazardous pesticides at hand, incidence of intentional pesticide poisonings is on the rise (WHO, 2009). According to an estimate the number of intentional cases alone reaches some 126,000 cases annually (Eddleston *et al.,* 2003; Eddleston, 2000).

Pathophysiology of OP poisoning:

Most of the ill-health following exposure to organophosphorus compounds has been attributed to the inhibition of cholinesterases. Acetylcholine is one of many neurotransmitters in the autonomic nervous system (ANS). It has functions both in the peripheral nervous system (PNS) and in the central nervous system (CNS) as a neuromodulator. In the peripheral nervous system, acetylcholine activates muscles, and is a major neurotransmitter in the autonomic nervous system. In the central nervous system, acetylcholine and the associated neurons form a neurotransmitter system, the cholinergic system, which tends to cause inhibitory actions. The normal function of Acetylcholinesterase (AChE) is to destroy acetylcholine in the synaptic cleft or neuromuscular junction. Failure of acetylcholinestrase activity results in accumulation of acetylcholine which inturn causes enhancement and prolongation of cholinergic effects and also depolarization blockade (Koelle, 1992). AChE has a very high catalytic activity and converts acetylcholine into the inactive metabolites choline and acetate. The high amount of released choline is transported back into the nerve ending for reconversion to acetylcholine and storage. Inhibition or degradation of acetylcholine is necessary in rapidly clearing free acetylcholine from the synapse which is essential for proper muscle function. The rate and degree of AChE inhibition is dependent on the structure of the OP and the extent of exposure (Abroug, 2007).

Certain neurotoxins work by inhibiting acetylcholinesterase, thus leading to excess acetylcholine at the neuromuscular junction, causing paralysis of the muscles. Organophosphates (OP), esters of phosphoric acid, are a class of irreversible AChE inhibitors. Irreversible inhibitors of AChE may lead to muscular paralysis, convulsions, bronchial constriction and death by asphyxiation (Nambda *et al.,* 1971). Exaggerated manifestations of nicotinic and muscarinic receptors appear as a result of these actions (Mortensen, 1986; Nambda *et al.,* 1971). It has been reported that toxic effects of organophosphates may not be limited to acetylcholinesterase inhibition, but oxidative stress could be a major factor in the pathophysiology of OP compounds (Pita *et al.,* 2013; Eddleston *et al.,* 2005). Organophosphorus poisoning exhibits the following classical phases in the affected patients. Acute organophosphate poisoning manifests three different phases of toxicity; namely, acute cholinergic crisis, which occurs from within a few minutes to twenty-four hours intermediate syndrome (IMS), which sets in 48 h to 96 h after exposure and delayed neuropathy which sets in after second phase (Yang and Deng, 2007).

The initial phase:

The inactivation of AChE by alkyl phosphorylation leads to accumulation of acetylcholine at the following locations. At muscarinic sites,it causes bronchorrhoea, (an increase in secretions salivation, tearing and sweating), bronchoconstriction (tightness in the chest and wheezing), bradycardia, (vomiting and an increase in gastrointestinal

motility) (abdominal tightness, cramps and diarrhoea). Exposure to organophosphates also causes the diagnostic miosis in the eye, which results in blurring of vision. At nicotinic sites (e.g. neuromuscular junctions), it results in muscle fasciculations and a flaccid paralysis in severe exposures. Within the central nervous system, it causes headache, insomnia, giddiness, confusion, drowsiness and, in severe exposures, slurred speech, convulsions, coma and respiratory depression (Johnson *et al.,* 2000). Excessive muscarinic receptor stimulation produces the classical manifestations of OP poisoning. The mnemonics SLUDGE (salivation, lacrimation, urination, diarrhea, gastrointestinal cramps, and emesis) and DUMBBELS (defecation, urination, miosis, bradycardia, bronchorrhea, emesis, lacrimation, and salivation) are used to recall some of these effects. Typically these symptoms are the first to develop (Seabury *et al.,* 2013).

The intermediate phase:

Intermediate syndrome is a state of muscle paralysis that occurs after recovery from cholinergic crisis but before the expected onset of the delayed polyneuropathy which probably results from post-synaptic neuromuscular junction dysfunction (Koelle, 1992)**.** This occurs 1–4 days after the acute cholinergic phase and is characterized by the onset of muscle weakness (proximal muscles of the limbs) and cranial nerve palsies. Difficulty in breathing may progress to respiratory failure following paralysis of the diaphragm and other muscles of respiration. Complete recovery occurs within 4–21 days after appropriate ventilatory care. Although the exact pathogenesis of the intermediate syndrome is unknown at present, there is probably altered function and activity of the nicotinic receptors at the neuromuscular junction (Faiz *et al.,* 2011). Some workers have attributed the intermediate syndrome to either inadequate or delayed oxime therapy (Midtling *et al*., 1985; Taylor, 1980). This phenomenon is more commonly known as "aging" and its rate is dependent on the structure.

However no seriously poisoned nerve agent casualty has been reported to have the intermediate syndrome that Senanayake and Karalliedde (1987) described as arising from pesticide exposure. Although organophosphate pesticides are less-potent inhibitors of AChE than nerve agents and have less-steep dose-response curves, the two groups share many features in common i.e. inhibiting AChE and other serine esterases and interacting with receptors similarly. It is important to gain from the human experience on organophosphate chemicals poisoning on farmer with the possibility of longer-term effects from seasonal low dose but continuous exposures and assessing effects from non exposures.

Delayed polyneuropathy

This syndrome appears 7–21 days after exposure to an organophosphorus agent and predominantly affects the long nerves or tracts in the nervous system causing symmetrical weakness of peripheral muscles in the hands and feet, with a variable degree of sensory impairment. Disability may be permanent, though recovery has taken place in a few instances (Taylor, 1980). Midtling *et al*. (1985) reported, exposure of 16 cauliflower workers poisoned by residues of the organophosphate insecticides Mevinphos. None had pre-exposure baseline values. However subsequent testing showed significant inhibition of erythrocyte activity. While the most severe symptoms of these subjects resolved after 28 days, their erythrocyte cholinesterase levels did not reach a plateau until an average of 66 days after exposure, after which most patients continued to

report blurred vision, headache, weakness or anorexia. These findings support the view that the diagnostic utility of single cholinesterase levels is limited in the absence of baseline values (Midtling *et al.*, 1985).

Other Notable effects of exposure:

A greater frequency of upper respiratory tract infections was demonstrated in workers occupationally exposed to organophosphates where a decrease in serum and red blood cell cholinesterase activity was observed (Senanayake and Karalliedde, 1987). Patients with occupational organophosphate exposure developed 'influenza-like' symptoms (Benson *et al.*, 1992) Hyperamylasaemia and acute pancreatitis have been reported after oral or dermal organophosphate exposure. The hyperamylasaemia was closely related to the clinical severity and the presence of shock. Cardiac complications are often associated with organophosphate poisoning, with the symptoms ranging from hypotension or hypertension to arrhythmias and cardiac arrest. A case of congestive cardiomyopathy has been reported following long-term organophosphate exposure (Johnson, 1969). Profuse and offensive diarrhoea often develops in patients following organophosphate ingestion. Animal data suggested that organophosphate poisoning may cause severe teratogenicity and, consequently, a termination of pregnancy following exposure in the first trimester. However, normal childbirth has been reported following severe poisoning in the second and third trimesters (Hermanowicz and Kossman, 1984). Long-term exposure to relatively low levels of organophosphate pesticides (OP) agents occurs in a variety of environments. Pesticides are often applied in a combination with several classes of compounds featuring synergistic interactions. Salvi *et al*. (2003) reported Neuropsychiatric Evaluation in tobacco field subjects chronically exposed to Organophosphate Pesticides. They opinioned that the study reinforces the need for parameters other than acetylcholinesterase activity to monitor for chronic consequences of chronic low-dose OP exposure, and it suggests that subjects have not only transient motor and psychiatric consequences while exposed, but may also develop enduring extrapyramidal symptoms.

Conventional counter measures:

Standard therapy involves attempts to reduce absorption with gastric lavage and/or activated charcoal, plus administration of atropine and oxime to counter the effects of absorbed pesticide (Eddleston, 2000; Ballantyne and Marrs, 1992). Patients with intermediate syndrome require optimal respiratory management, and treatment with atropine and pralidoxime (Yang and Deng, 2007). Organophosphorus pesticides inhibit acetylcholinesterase (AChE) at the muscarinic and nicotinic synapses by depositing a phosphoryl group at the enzyme's active site. This results in an accumulation of acetylcholine and uncontrolled activation of cholinergic synapses. Standard therapy involves attempts to reduce absorption with gastric lavage and/or activated charcoal, plus administration of atropine and oxime to counter the effects of absorbed pesticide. The use of high doses of atropine is well established but the use of oximes more controversial (Seabury *et al.*, 2013; Johnson *et al.*, 2000). Atropine is a muscarinic cholinergic antagonist. It acts by blocking the effects of the acetylcholine that accumulates at muscaranic sites as a consequence of the anticholinesterase actions of the nerve agents and has little effect at nicotinic sites. Oximes reactivate acetylcholinesterase by

removing the phosphoryl group. Pralidoxime is the oxime most often used worldwide and occurs in four forms: pralidoxime chloride (2-PAM; molecular weight 173; used worldwide), pralidoximemesylate (P2S; MW 232; used in the UK), pralidoxime metilsulfate (MW 248) and pralidoxime iodide (MW 264; used in Japan, India & Australia) (Worek *et al.,* 1997). The great majority of its effects are on the peripheral nervous system since its lipid solubility is low and entry into the CNS limited.Atropine works at muscarinic synapses, competitively antagonising the accumulated acetylcholine.

Pralidoxime:

Pralidoxime is an oxime, a chemical that reacts with the nerve agent-inhibited cholinesterase enzyme to remove the nerve agent from the enzyme, allowing acetylcholinesterase to break down acetylcholine. Timing of pralidoxime administration is critical because the binding of the nerve agents to acholinesterase can become irreversible with time. This irreversible binding is called "aging." Once aging has occurred, the cholinesterase enzyme will be unable to break down acetylcholine. Aging occurs at different rates for different nerve agents. The optimal dosage is dependent on the nerve agent, time since exposure, and the cholinesterase activity of the victim. One human study assessed regeneration of cholinesterase activity when IV pralidoxime was given one hour after sarin exposure: A pralidoxime dosage of 10 mg/kg reactivated 28% of RBC cholinesterase activity. A pralidoxime dosage 20 mg/kg reactivated 58% of RBC cholinesterase activity.

In vitro experiments have shown that oximes are effective reactivators of human AChE inhibited by OP compounds. Reactivation of inhibited AChE by oximes is likely be absent or limited, in certain situations like, poor affinity for the particular OP-AChE complex; insufficient dose or duration of treatment; persistence of the OP within the patient and therefore rapid re-inhibition of newly reactivated enzyme and ageing of the inhibited AChE be avoided (Benson *et al*., 1992; Willems *et al.,* 1993; Thiermann *et al.,* 1999). Sundwall reported that the minimum effective plasma concentration of P2S was 4 mg/L in cats poisoned with a quaternary analogue of the nerve agent sarin (Sundwall, 1961). This result has since been uncritically extrapolated to all oxime and OP interactions. It has now become clear, however, that the degree of reactivation is dependent on the specific identity and concentrations of both oxime and OP (Salvi *et al.,* 2006; Benson *et al*., 1992). For example, most OP pesticides can be classified as compounds that form either a dimethylphosphoryl- or a diethylphosphoryl- AChE complex. *In vitro* studies have shown that while seven times as much pralidoxime as obidoxime is required for reactivation of dimethyl-OP inhibited AChE, diethyl-OPs require 20 times more pralidoxime than obidoxime (Thiermann *et al.,* 1999). Diethyl-OP inhibited AChEs both reactivate and age significantly slower than the dimethyl analogues (Kumar *et al.,* 2010).

Clinical features:

Since the early signs and symptoms of nerve agents and those of organophosphate pesticides are identical, there is no clear differentiation between them at the clinical level. Classification of signs and symptoms of acute organophosphate poisoning according to receptor site and type is given in the Table I (Maynard and Beswick, 1992).

Table 1. Clinical Manifestations of OP poisoning according to receptor type

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

Clinical management:

Sidell *et al.* (1997) emphasized the rapid onset of nerve agent effects (acute toxicity) compared with those of organophosphate pesticides (chronic exposure) and noted the longer and more-difficult-to treat course of serious organophosphate pesticide poisoning. The acute toxic dose in human is not known with any exactitude (Maynard and Beswick, 1992). Therefore lethal doses and likely clinical effects in human have to be inferred from experimental data on poisoning in animals and from OP pesticide poisoning. Despite organophosphates being a common poisoning only one antidote, atropine for OP poisoning, could be clearly regarded as effective. The efficacy of oximes remains to be defined and relies on understanding of the reasons for treatment failure. Management consists of proper oxygenation, atropine in escalating doses and pralidoxime in high doses. It is important to decontaminate the skin while taking precautions to avoid secondary contamination of health personnel. Organochlorine pesticides are toxic to the central nervous system and sensitize the myocardium to catecholamines. Treatment involves supportive care and avoiding exogenous sympathomimetic agents. Poisoning Treatment ParadigmTM (https://www.clintox.org/.../).

A = Alter Absorption

For skin contact with liquid nerve agents, ensure the patient has been undressed and adequately decontaminated in the field with soap or a mild liquid detergent and water. If soap or a mild liquid detergent is not immediately available, do not delay decontamination with water.

A = Administer Antidote

Atropine:

Atropine is a symptomatic antidote for the muscarinic signs and symptoms of nerve agent poisonings. Atropine is a competitive antagonist at muscarinic receptors only. It blocks

the effects of acetylcholine at muscarinic receptors in the PNS and CNS. Therefore, atropine is a parasympatholytic, in other words, it is "anti-DUMBELS." Atropine works only at the muscarinic receptors and cannot counteract acetylcholine's effects at nicotinic receptors in the PNS or CNS. Therefore, atropine cannot counteract
fasciculations, weakness, flaccid paralysis, or respiratory arrest that is due to neuromuscular blockade at nicotinic receptors. Atropine competitively antagonizes acetylcholine's binding only at muscarinic receptors. Atropine does not regenerate the poisoned acetylcholinesterase, i.e., it does not reactivate the inactivated acetylcholinesterase, i.e., it is not curative. The total doses of atropine for nerve agent poisoning are often much smaller than those needed to treat organophosphate insecticide poisoning. Organophosphate insecticides are more slowly metabolized and more lipid soluble. Consequently, they are cleared much more slowly from the body; therefore, the cumulative dose of atropine can reach much higher totals. "Mild" exposures resulting only in miosis and do not require atropine because atropine does not reverse miosis, and it can cause other problems because of its anticholinergic effects. Miosis and ciliary spasm with severe eye pain can be treated with topical homatropine ophthalmic drops, if necessary. Rhinorrhea (runny nose) alone generally does not merit atropine administration, unless it is severe and interferes with the patient management. In severe cases of nerve agent poisoning, atropine should be given until ventilation is easy and respiratory secretions have dried. If true cholinergic excess exists, the administration of atropine should produce no ill effects. Excessive amounts of atropine, from giving too much to a symptomatic patient or from giving atropine to an unexposed person, can produce anticholinergic effects. These include dry mouth, blurred vision, dilated pupils, urinary retention, tachycardia, and inability to sweat. These side effects are generally considered minor, but can last for 24 to 48 hours.
Significant caution should be exercised when hypoxia is present in cases of severe nerve agent poisoning. Intravenous administration of atropine to animals with hypoxia due to severe respiratory complications of nerve agent poisoning has produced ventricular fibrillation. Therefore, hypoxia should first be corrected, if possible, before atropine is administered. However, atropine should not be withheld from a victim of severe nerve poisoning because of a concern about precipitating a life-threatening arrhythmia, especially if the victim is an apparently healthy young person with an otherwise healthy heart.

Beyond the conventional:
There has been little clinical development of a large number of low cost antidotes that have been shown to be effective in animals and which could be clinically useful. Such antidotes need to be accessible and affordable. Drugs that fulfill these criteria include: sodium bicarbonate, clonidine, magnesium and diazepam. All of these have a good biological rationale, positive evidence from animal studies (Murphy *et al.,* 1993; Liu, 1991; Cordoba *et al.,* 1983) and have been used in humans for many years. Recently a number of trials have been underway to try and define the role of such potential antidotes. Arguably this requires the use of validated intermediate outcomes in addition to outcomes such as death and ventilation. Putative mechanisms for such antidotes include direct alterations in pesticide kinetics such altered binding, enhanced clearance and alterations in the pharmacodynamics of the OP-cholinesterase complex. Alternate strategies include

alteration in synaptic acetylcholine release. Both Magnesium and Clonidine reduces acetylcholine synaptic concentration. Diazepam appears to reduce centrally mediated respiratory failure in animals and had synergistic activity with anticholinergics. Treatment with intravenous sodium bicarbonate had been reported to be protective in some animal models and anecdotally in humans. A recent study demonstrated that sodium bicarbonate in a dose of that 5 mEq/Kg of over 60 minutes followed by 5-6 mEq/Kg over 24 hours could safely alkalinize patients and reduce bed stay (Mumford *et al.*, 2013; Pan *et al.*, 2012; Soltaninejad and Abdollahi, 2009).

Benzodiazepines are used to control OP induced seizures. In warfare, alongside regular therapy, pre-treatment with pyridostigmine is recommended. Some of the non-regular antidotes include clonidine, fresh frozen plasma, magnesium sulphate, N-acetylcysteine activated charcoal, milk and certain other home remedies, but their effectiveness has not yet been sufficiently established. Soltaninejad and Abdollahi (2009) listed several (106 Nos) studies conducted on various animal /experimental models between 1977 and 2008 on the toxic response of different types of OP compounds and treatment with non-conventional drugs like Vitamin E & C , Melatonin, Green tea extracts, Zinc Chloride, Ginger, copper etc. Each one of these gave certain positive response against OP compounds on animal and experimental models. Other experimental approaches include the use of NMDA receptor antagonists such as gacyclidine, haemoperfusion and the nanocarrier of magnetic magnesium. Non-regular antidotes for some reason usually do not receive attention from the scientific community, so the related scientific reports are negligible. Approaches such as the alkalization of blood plasma, use of weak inhibitors against strong inhibitors or use of bioscavengers are very popular but have not gained validity. The clinical role of these antidotes is still being defined but it is likely that some will find a therapeutic role.

CONCLUSIONS

The ubiquitous organophosphates present a continuing health hazard for agriculture workers and as chemical warfare agents. Despite significant progress in understanding the potential mechanisms of toxicity and the precise health effects following occupational exposures are yet to be completely defined. Presently these are characterized by a triphasic response involving an initial acute cholinergic phase, an intermediate syndrome (both associated with high mortality) and a disabling but non-lethal delayed polyneuropathy. The delayed polyneuropathy may occur in the absence of the cholinergic or intermediate phases. However, progress is still required in order to improve the quantification and assessment of occupational exposures and the implementation of appropriate preventive measures. Since the mortality rate of OP poisoning is high and the fatal issue is often related to a delay in diagnosis or an improper management. Early diagnosis and appropriate treatment are often life saving, although the clinical course of OP poisonings might be quite severe and necessitate intensive care management. As in all cases of poisoning, the exposed person should be removed as soon as possible from the source of contamination and decontaminated. Since respiratory failure is the major reason for mortality, careful monitoring, appropriate management and early recognition of this complication may decrease the mortality rate among these patients. Patients with OP poisoning may have respiratory failure for many reasons, including aspiration of gastric contents, excessive secretions, pneumonia and septicemia complicating adult

respiratory distress syndrome. Aspiration pneumonia is another troublesome complication, and careful monitoring during transport and early recognition of an absent gag reflex may reduce the incidence of aspiration pneumonia. Early recognition of respiratory failure, prompt endotracheal intubation and mechanical ventilation are life-saving measures in severe OP poisoning.

References

Abroug, F. (2007) High-dose pralidoxime for organophosphorus poisoning. *Lancet* 369: pp. 1426–1427.

Ashish, G., Praveen, A. (2007) Pesticide poisoning. *The National Medical Journal of India,* Vol. 20, 4: pp. 182-191

Bajgar, J. (2004) Organophosphates/nerve agent poisoning: Mechanism of action, diagnosis, prophylaxis, and treatment. *Adv Clin Chem* Vol. 38: pp.151-216.

Ballantyne, B., Marrs, T. C. (1992) Overview of the biological and clinical aspects of organophosphates and carbamates. In: Ballantyne B, Marrs TC, eds. *Clinical and experimental toxicology of organophosphates and carbamates.* Butterworth-Heinemann: Oxford Press: pp. 3-14.

Benson, B., Tolo, D., McIntire, M. (1992) Is the intermediate syndrome in organophosphate poisoning the result of insufficient oxime therapy? *J Toxicol Clin Toxicol*, 30: pp. 347-349.

Cordoba, D., Cadavid, S., Angulo, D., Ramos, I. (1983) Organophosphate poisoning. *Vet Hum Toxicol,* 25(1): pp. 1-3.

Eddleston, M., Eyer, P., Worek, F., Mohamed, F., Senarathna, L, von Meyer, L. (2005) Differences between organophosphorus insecticides in human self-poisoning: A prospective cohort study. *Lancet* , 366: pp. 1452–1459.

Eddleston, M., Singh, S., Buckley, N. (2003) Acute organophosphorus poisoning. *Clinical Evidence,* Vol. 9: pp. 1542–1553.

Eddleston, M. (2000) Pattern & Problems of Deliberate self-Poisoning in the developing world. QJM 93: pp. 715-731.

Erdman, A. R. (2004) Insecticides. In: Dart RC (ed). *Medical toxicology.* 3rd ed. Philadelphia, PA: Lippincott Williams and Wilkins: pp. 1475-1496.

Faiz, M. S., Shaheen Mughal, Sh., Memon, A. Q. (2011) Acute and Late Complications of Organophosphate Poisoning, *Journal of the College of Physicians and Surgeons Pakistan,* , Vol. 21 (5): pp. 288-290.

Hermanowicz, A., Kossman, S. (1984) Neutrophil function and infectious disease in workers occupationally exposed to phosphoorganic pesticides: role of mononuclear-derived chemotactic factor for neutrophils. *Clin Immunol Pathol,* 33: pp. 13–22.

https://www.clintox.org/.../Ch28 Chemoterrorism: Nerve Agents.

Johnson, M. K, Jacobsen, D., Meredith, T. J., Eyer, P., Heath, A. J., Ligtenstein, D. A., Marrs, T. C., Szinicz, L., Vale, J. A., Haines, J. A. (2000) Evaluation of antidotes for poisoning by organophosphorus pesticides. *Emergency Medicine* 12(1): pp. 22–37. [MEDLINE: 10411].

Johnson, M. K. (1969) The delayed neurotoxic effect of some organophosphorus compounds. *Biochem J,* 14: pp. 711–717.

Karalliedde, L., Edwards, P., Marrs, T, C. (2003) Variables Influencing the Toxicity of organophosphates in humans. *Food Chem Toxicol,* Vol. 41: pp. 1–13.

Karalliedde, L., Eddleston, M., Murray, V. (2001) The global picture of organophosphate insecticide poisoning. In: Karalliedde L, Feldman F, Henry J, Marrs T, eds. *Organophosphates and health*. London: Imperial College Press: pp. 431-473.

Karczmar, A. G. (1970) History of the research with anticholinesterase agents. In: Karczmar A G, Usdin E, Wills J H, eds. *Anticholinesterase agents,* Oxford: Pergamon Press: pp. 1-44.

Koelle, G. B. (1992) Pharmacology and toxicology of organophosphates. *In Clinical and Experimental Toxicology of Organophosphates and Carbamates* (Ballantyne, B. and Marrs, T. C. *Eds.*) Oxford: Butterworth-Heinemann: pp. 33-37.

Kumar, S. V., Fareedullah, M. D., Sudhakar, Y., Venkateswarlu, B., Kumar, A. E. (2010) Current review on organophosphorus poisoning. *Archives of Applied Science Research*, 2 (4): pp. 199-215.

Liu, W. F. (1991) A symptomatological assessment of organophosphate-induced lethality in mice: comparison of atropine and clonidine protection. *Toxicol Lett*, 56(1-2): pp. 19-32.

Marrs, T. C., Marynard, R. L., Sidell, F. R. (1996) *Chemical Warfare Agents; Toxicology and Treatment* , John Wiley & Sons 1996.

Maynard, R. L., Beswick, F. W. (1992) Organophosphorous compounds as chemical warfare agents. In: *Clinical and Experimental Toxicology of Organophosphorous and Carbamates* (B. Ballantyne and T. C. Marrs Eds.) Oxford: Butterworth-Heinemann: pp. 373-385.

Midtling, J. E., Barnett, P. G., Coye, M. J. (1985) Clinical management of field worker organophosphate poisoning. *West J Med* 142: pp. 514-518.

Mortensen, M. L. (1986) Management of acute childhood poisoning caused by selected insecticides and herbicides. *Pediatr Clin North Am*, 33: pp. 421–445.

Moretto, A., Lotti, M. (2001) Monitoring of occupational exposures to organophosphorus compounds. In: Karalliedde, L., Feldman, S., Henry, J., Marrs, T. C. eds. *Organophosphates and Health*. Imperial College Press, 2001.

Mumford, H., Docx, C. J., Price, M. E., Green, A. C., Tattersall, J. E., Armstrong, S. J. (2013) Human plasma-derived BuChE as a stoichiometric bioscavenger for treatment of nerve agent poisoning. *Chem Biol Interact*, 25: 203(1): pp. 160-166.

Murphy, M. R., Blick, D. W., Dunn, M. A., Fanton, J. W., Hartgraves, S. L. (1993) Diazepam as a treatment for nerve agent poisoning in primates. *Aviat Space Environ Med*, 64(2): pp. 110-115.

Namba, T., Nolte, C. T., Jackrel, J., Grob, D. (1971) Poisoning due to organophosphate insecticides. Acute and chronic manifestations. *Am. J. Med.*, 50: pp. 475–492.

Pan, H., Hu, X. Z., Jacobowitz, D.M., Chen, C., McDonough, J., Van Shura, K., Lyman, M., Marini, A. M. (2012) Alpha-linolenic acid is a potent neuroprotective agent against Soman-induced neuropathology. *Neurotoxicology*. Oct. 33(5): pp. 1219-1229.

Pita, R., Marco-Contelles, J., Ramos, E., del Pinto, J., Ramero, A. (2013) *Arch Toxicology*, Guest Editorial, Springer-Verlag, 8th July 2013.

Reddy, K. S. (2006) *The Essentials of Forensic Medicine and Toxicology*. 25th ed. India: Medical Book Co, 2006.

Rodgers, M. L. (2006) OP poisoning. *Am. J. Emerg. Med.* Vol. 22: pp. 335-344.

Salvi, R. M., Lara, D. R., Ghisolfi, E. S., Portela, L. V, Dias, R. D., Souza, D.O. (2003) Neuropsychiatric Evaluation in Subjects Chronically Exposed to Organophosphate Pesticides, *Toxicological Science* 72: pp. 267–271.

Seabury, R. W., Pharm, D., Ross Sullivan, M. D., Stork, C. M. (2013) The Persistent Pesticide: A Review of Organophosphate Poisoning, *Toxicology Letters* Vol. XVIII No.1:1-9.

Senanayake, N., Karalliedde, L. (1987) Neurotoxic effects of organophosphorus insecticides: an intermediate syndrome. *N Engl J Med*; 316: pp. 761-776.

Sidell, F. R.,Takafugi, E. T., Franz, D. R. (1997) Nerve Agents in Medical Aspects of Chemical & Biological Warfare (Sidell, F. R., Takafugi, E.T. & Franz, D. R. (eds). *Weapons and Casuality.* Washington DC. US Department of the Army. Office of surgeon General & Borden Institute, 1997.

Soltaninejad, K., Abdollahi, M. (2009) Current opinion on the science of organophosphate pesticides and toxic stress: a systemic review. *Med Sci Monit*, 15: RA: pp. 75-90.

Somani, S. M. (1992) *Chemical Warfare Agents*: Academic Press Inc. 1992 USA.

Sundwall, A. (1961) Minimum concentrations of N-methylpyridinium-2- aldoxime methane sulphonate (P2S) which reverse neuromuscular Oximes for acute organophosphate pesticide poisoning (Review) Copyright © 2008 The Cochrane Collaboration. Published by JohnWiley & Sons, Ltd.junction block. *Biochemical Pharmacology*, 8: pp. 413–17.

Taylor, P. (1980) Anticholinesterase agents. In: Goodman LS, Gilman A, editors. The pharmacological basis of therapeutics. 6th ed. New York: *MacMillan Publishing Co*: p. 428.

Thiermann, H., Szinicz, L., Eyer, F., Worek, F., Eyer, P., Felgenhauer, N., Zilker, N. (1999) Modern strategies in therapy of organophosphate poisoning. *Toxicology Letters* 107(1-3): pp. 233-239.

Vijayaraghavan, R., Ganesan, K., & Raza, S. K. (2010) Chemical warfare agents. *J Pharm Bioall Sci Vol.* 2: pp. 166-178.

WHO. (2009) Health implications from monocrotophos use: a review of the evidence in India – WHO 2009: pp. 1-6.

Willems, J. L., De Bisschop, H. C., Verstraete, A. G., Declerck, C., Christiaens, Y., Vanscheeuwyck, P., Buylaert, W. A., Vogelaers, D., Colardyn, F. (1993) Cholinesterase reactivation in organophosphorus poisoned patients depends on the plasma concentrations of the oxime pralidoxime methylsulphate and of the organophosphate. *Archives of Toxicology*, 67: pp. 79-84.

Worek, F., Backer, M., Thiermann, H., Szinicz, L., Mast, U., Klimmek, R., Eyer, P. (1997) Reappraisal of indications and limitations of oxime therapy in organophosphate poisoning. *Human and Experimental Toxicology*, 16 (8): pp. 466-472.

Yang, C. C., Deng, J. F. (2007) Intermediate syndrome following organophosphate insecticide poisoning. *J Chin Med Assoc*, 70: pp. 467-472.