

ORGANOPHOSPHORUS POISONING – REVISITED

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Abstract: Organophosphorus (OP) compound was synthesized about one and half century ago in France. Tetraethyl pyrophosphate (TEPP) was the first to be manufactured in liquid form in 1950. Since then numerous compounds have been synthesized and used as agricultural insecticides. They are easily available in the market on account of inadequate regulations controlling their use and storage. OP pesticide intoxications are estimated at 3 million per year worldwide with approximately 3,00,000 deaths. The fatality rate following deliberate ingestion of OP pesticides in developing countries in Asia is about 2% and may reach as high as 70% during certain seasons and at rural hospitals. More than 100 OP compounds are currently available under different brand names. Acute poisoning in human occurs due to suicidal ingestion and accidental exposure while spraying. Ops inactivate acetyl-cholinesterase (AChE) by phosphorylation leading to accumulation of acetylcholine (ACh) at cholinergic synapses. Recovery follows the reappearance of active AChE following synthesis or spontaneous hydrolysis of phosphorylated AChE. The phosphorylated AChE may lose a chemical group so that its inactivation becomes irreversible; this is well known as compared to diethyl compounds. Sequential triphasic illness follows OP intoxication starting from acute cholinergic phase to intermediate syndrome resulting in organophosphate induced delayed polyneuropathy. Cholinesterase (che) estimation (plasma butyryl cholinesterase and red cell AChE) are the only useful biochemical tools for confirming exposure to Ops, but are a poor guide to management and prognosis. Regarding management, complete and early atropinisation is essential in early management and treatment should be started immediately on clinical grounds without waiting for laboratory investigations. Speed of administration is as important as use of sufficient doses. Oximes have a definite role and a response should be seen within 30 minutes with resolution of fasciculation, convulsion muscle weakness and coma. Ventilatory support should be instituted before a patient develops respiratory failure. The need of the hour is framing of regulations by the govt. of India controlling the use and storage of Ops.

Key words: Organophosphorus compound, acetyl cholinesterase; atropinisation; oximes

INTRODUCTION

The commonest poisoning in India is with pesticides, most commonly organophosphate compounds (OPC) on account of their ready and easy availability in the market since there are inadequate regulations controlling their use and storage. Acute OPC poisoning is a major health problem¹. Poisoning is seldom included as a priority for health research India, though every year, hundreds of people are losing their life prematurely for pesticide poisoning. According to WHO, it is estimated that 3 million cases of pesticide poisoning with 2000 deaths every year occur world wide particularly in developing countries^{1,2,3}. Organophosphate compounds (OPC) are common insecticide exclusively used by farmers. More than 100 OP compounds are currently available under different brand names, so that their identification becomes very difficult until/unless the patient's relative/family members bring the said container to the doctor^{1,3}. The pesticides include *organophosphorus compounds* and *carbamates*. Quite often the victim is brought to the doctor within an hour of consumption of the pesticide. This is the *'golden hour'* for clinical intervention, before irreversible "ageing" of toxic compounds in blood occurs.^{4,5} OP compounds have been in use for pest control since many years and unfortunately are common agents of suicidal and accidental poisoning.^{6,7} Highly toxic agricultural insecticides like TEPP (Tetraethyl-pyrophosphate) was used as a nerve gas in chemical warfare during world war II by Germany^{8,9}. The use of OP compounds as nerve gas agents has been banned by Geneva Convention in 1974 as part of a large ban in chemical warfare. However they have been used in recent wars in Iraq and Tokyo⁹. Among OP group, the most common cause of human poisoning and fatality is with the use of parathion and the mortality varies from 7-12%. Less commonly used and less

toxic Ops have now almost replaced; DDT, an organochloride compound thus becoming popular insecticide¹². Majority of cases (60-70) of OP poisoning result from suicidal ingestion^{13,14}. Accidental and occupational exposure such as spraying of crops are less routes of poisoning^{15,16}.

CLASSIFICATION OF ORGANOPHOSPHATES

A. Based on clinical toxicity⁴:

- Highly toxic:** Agricultural insecticides e.g. i) TEPP ii) Parathion-symptoms toxicity occur late by -24 hrs because it has to be converted in to paraxon iii) phorate iv) disulfoton v) mevinphos
- Intermediate toxic:** animal Insecticides e.g. cholor-pyrifos, trichlorfos, coumaphos.
- Low toxicity:** Household use .e.g. malathion, dichlorovos, diazinon and carbamate insecticides which include aldicarb, propoxur (Baygon), Carbaryl and bendiocarb (Ficam) Therapeutic carbamates include ambenonium, neostigmine, physostigmine and pyridostigmine. The commonly available products are methyl parathion (Folidol, Paramar, Metacid, Paramet), malathion (malathion, Cythion) and phallone (Zolone, sumithion Faithion, Timidan, Ektakin).

B. Based on pharmacokinetics⁴:

Organophosphorus compounds and carbamates are a family of compound that share structural similarities. The kinetics of each group are highly dependant on multiple factors like onset, duration and severity of poisoning, route of administration (ingestion, injection, inhalation, transdermal and transmucosal absorption), distance from target organs, local versus systemic metabolism and activation, route of elimination, endogenous hydrolysis and consumption of the compound by various nonspecific esterases before reaching target organs. Structural consideration includes the group attached to the

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sulfur, carbon or phosphorus moiety, the tightness of the bond to the central atom and the affinity of the compound for cholinesterases.

C. Based on characteristics of compound:

1. **Nature of compound** i) *Water soluble*: Effects are acute and short lived e.g. tepp. ii) *Liquid soluble*: Effects are chronic and of longer duration e.g. Chlor-fenthion, fenthion, difenthion
2. **Mode of action**
 - i) **Direct agent** - directly inhibits acetyl-cholinesterase e.g.
 - ii) **Irreversible** - has to be converted in to active metabolite metabolite e.g. parathion
3. **Type of binding**
 - i) **Reversible** - effects are acute and short lived
 - ii) **Irreversible** - effects are more sustained e.g. parathion
4. **Route/Severity of Exposure**
 - i) Oral/GIT - acute toxicity
 - ii) Skin - acute toxicity
 - iii) Inhaled - acute on chronic
5. **Toxicity of the poison**
 - i) High
 - ii) Intermediate

The fat soluble compounds may not manifest toxicity for several days to weeks because the toxic substance must be "leached out" of the fat until sufficient amount of cholinesterase is inhibited to cause symptoms.

PATHOPHYSIOLOGY OF OP POISONING

The major neurotransmitter in CNS released by the terminal nerve endings of all the postganglionic parasympathetic nerves and in both sympathetic as well as parasympathetic ganglia is the acetylcholine (ach). Other sites of ach release are neuromuscular junctions. The enzyme acetyl-cholinesterase exists in 2 forms (a) *true cholinesterase* mainly present in the nervous tissues and RBCs (b) *pseudo-cholinesterase* present in liver and serum only.⁷

Ops bind to the active serine residue of acetylcholinesterase irreversibly and convert the enzyme into inactive protein complex, resulting in excessive accumulation of Ach at the synapses / receptors. This results in over stimulation and subsequent disruption of nerve impulse transmission in both the brain as well as sympathetic and parasympathic system.

Over a period of time organophosphate compounds can permanently affect the acyl pocket so that endogenous hydrolysis of the serine phosphate bond can not occur and antidote function becomes limited. This is called "ageing". During the "ageing reaction" the acyl group is lost from the phosphorylated enzyme and the pocket shape change becomes permanent. Carbamates dissociate from Ache molecule within 24 hours, so they do not causing limited CNS toxicity.

Most Ops are well absorbed from skin, GIT, lungs, oral and conjunctival mucous membranes. After absorption, they are hydrolyzed by enzymes e.g. esterases or paroxenases, which are not inhibited by OP compounds. Then their metabolic products are excreted in the urine. Ops binding to acetylcholinesterase (ach-ase) inhibit the conversion of acetylcholine (Ach) to its degradation products like acetic acid and choline. This results in excessive accumulation of Ach at synapses, which becomes the root cause of toxicity of OP compounds.

CLINICAL MANIFESTATIONS OF OP POISONING (CHOLONERGIC CRISIS)

Signs and symptoms of acute poisoning occur within 24 hours of ingestion of OP compound. Toxicity due to carbamates is shorter in duration and usually less severe than that due to organophosphates

Muscarinic Effects i) *Ocular*: pinpoint pupils, blurring of vision, increased lacrimation. ii) *Respiratory* rhinorrhoea, dyspnoea, bronchorrhoea laryngeal spasm, bronchospasm, wheezing cough respiratory depression and pulmonary edema (due to uncontrollable bronchorrhoea)

iii) *CVS*: bradycardia, hypotension, arrhythmias including multiple ectopics, junctional rhythms and AV block. iv) *GIT* excessive salivation, nausea, vomiting, abdominal pain, diarrhea, fecal incontinence iv) *Genitourinary*: urinary frequency and incontinence vi) *CNS*: impaired consciousness, bilateral hyperreflexia, extensor plantar response vii) *Skin*: increased sweating.

Nicotinic effects: Musculoskeletal weakness

Fasciculations, twitching, cramps, paralysis ii) *CVS* tachycardia, hypertension, iii) *respiratory*: weakness paralysis of respiratory and oropharyngeal muscles and finally respiratory arrest.

Central receptor stimulation These features characterize isomnia, anxiety, convulsions, restlessness, coma, hyperreflexia, Cheyne strokes breathing, circulatory collapse and respiratory depression^{15,16}.

Neurological manifestations in OP poisoning most commonly result in the following effects

(A) **Type-I paralysis or acute paralysis**: It appears within 24-28 hours resulting from inhibition of enzyme acetylcholinesterase. It is characterized by fasciculations, cramps twitching and weakness of muscles and these features respond to atropine 16. Muscle paralysis may also invoke respiratory muscles resulting in acute respiratory failure in 33# patients.

(B) **Type-II Paralysis or Intermediate Syndrome or Wadia Syndrome**: This term was first coined by Wadia and later on by Senanayake¹⁸ since then many authors have described this clinical entity^{16,19,20,21}. This syndrome develops after the acute cholinergic crisis, 24-96 hours after the poisoning i.e. development of signs of paralysis appearing after admission and before the delayed neurotoxicity sets in; the incidence of this syndrome is 8% - 49%^{19,21,22,23}. Majority of the patients present with respiratory insufficiency, cranial nerve palsies and proximal muscle weakness. The presentation of these patients usually starts with marked weakness of neck flexion resulting in inability to lift the head from the pillow and inability to sit up. The common cranial nerves involved are those supplying the extra-ocular muscles resulting in to ophthalmoparesis and slow eye movements. Cranial nerves VII and X are least affected. Wadia⁶ in a study of 350 cases of OP poisoning reported 87 patients as having inability to lift neck, 99 patients having inability to sit, up 27 patients having ophthalmoparesis, 39 patients slow eye movement, 2 patients facial weakness, 14 patients swallowing difficulty, 86 patients proximal limb weakness, 52 as are flexia, 37 as respiratory failure and 33 died. *Nerve conduction and EMG studies* show that the primary type of involvement is an axonal neuropathy.^{24,25,26} This syndrome is also due to anterior cell or toxin induced muscular instability. It lasts for about 4-18 days and most patients survive this period with the use of mechanical ventilation

(C.) Type-II Paralysis or OP induced delayed Polyneuropathy:

It is a sensory motor distal axonopathy which appears with ingestion of certain Ops like triortho-cresylphosphate (70 CP) and tricesylphosphate (TCP).^{27,28,29} It develops usually 2-3 weeks after the acute poisoning episode and is characterized by distal muscle weakness with sparing of neck muscle, cranial nerves and proximal muscles. These patients show a pure motor axonal neuropathy with wrist drop and foot but no sensory loss. Usually the pyramidal tracts in the spinal cord are involved resulting in brisk tendon reflexes and spasticity. It is probably due to depression of a different esterase called neurotoxic esterase or neuropathic target esterase (NTE) in the nervous system and this form of toxicity occurs in small epidemics in India due to adulteration of cooking oil with TOCP6. The EMG studies suggest denervation and recovery is delayed up to 6-12 months²⁶.

Other neurological manifestations/neuropsychiatric features, especially occurring in chronic poisoning³⁰ are usually short lived and include irritability, confusion, lethargy, impaired memory and psychosis. Extra pyramidal manifestations³¹ usually appear after 4-40 days following poisoning in the form of resting tremors, dystonias, cog-wheel rigidity and choreoathetosis. Neuro-ophthalmological sequelae seen in chronic poisoning include retinal degeneration, optic atrophy, myopia due to spasm or paresis of accommodation³². Other rare neurological manifestations include isolated bilateral recurrent laryngeal nerve paralysis³³, sphincter involvement³⁴, Gullain-Barre syndrome³⁵ and ototoxicity³⁶.

Cardiovascular Manifestations: Saadh et al³⁷ reported various cardiac manifestations in the form of sinus tachycardia (35%), sinus bradycardia (28%), atrial fibrillation (9%), ventricular tachycardia (4%), extrasystole (6%), ST segment elevation (24%), inverted T waves (17%). Cardiac toxicity is due to direct toxic effect on the myocardium, hypoxemia, acidosis, electrolyte disturbances, over activity of nicotinic or cholinergic receptors as well as high dose atropine therapy.

Respiratory Manifestations

They occur in the form of rhinorrhoea, bronchorrhea, bronchospasm, laryngeal spasm, airway obstruction, paralysis of respiratory and oropharyngeal muscles. Even respiratory failure/arrest may occur¹⁷.

Gastrointestinal Manifestations

They occur in the form of nausea, vomiting and diarrhea. Rarely acute pancreatitis³⁸ and hypoglycemia³⁹ may occur.

DIAGNOSIS OF OP POISONING

The diagnosis is based on H/o ingestion or exposure to spray and combination of clinical features in the form of vomiting, diarrhea, pin pointed pupils, muscle fasciculations and proximal muscle weakness. measurement of plasma or serum red cells ChE levels are diagnostic. True and pseudo cholinesterase levels can be measured these levels are markedly reduced in OP poisoning True ChE levels usually correlate with severity at presentation but pseudo cholinesterase levels do not⁴⁰. Plasma cholinesterase levels are also reduced in other diseases like metastatic carcinoma, alcoholism, malnutrition, congestive heart failure with hepatomegaly and dermatomyositis. A 25% or greater reduction (less than 50%) in RBC cholinesterase level in diagnostic of OP poisoning¹². Other useful test is resistance to atropine action If

1.8 2.4 mg atropine does not cause significant tachycardia or papillary dilatation diagnosis is always certain¹⁰. Post mortem study shows cerebral edema in early cases. Some poison centers can identify the compound from the stomach contents.

Grading of severity of OP Poisoning Bardin et al⁴¹ validated a 3-grade system for poisoning at the time of admission

- i) *Mild poisoning*: History of intake/exposure, normal consciousness with mild increase in secretions and fasciculations.
- ii) *Severe poisoning*: Altered sensorium with excessive secretions and multiple fasciculations.
- iv) *Life threatening poisoning*: Suicidal attempt, stupor, abnormal chest roentgenogram and PaO₂ < 60 mm Hg. These groups of patients usually require mechanical ventilation with prior treatment in the form of atropine, suction and clearing of airway.

MANAGEMENT

Treatment should be started immediately on clinical grounds without waiting for laboratory investigations.

1. Non pharmacological treatment (General measures)

- a) *Decontamination*: Thorough decontamination of the skin with soap and water and subsequently with ethyl alcohol after removing all clothes of the patients in very important in order to prevent further absorption through the skin. Gastric decontamination is either done by forced emesis or through a gastric lavage is further facilitated with the addition of a new drug—serotonin adipinate, which increases the propulsive function of the GIT, resulting in shortening of the toxigenic phase and reduction in mortality⁴².

PHARMACOLOGICAL TREATMENT (SPECIFIC THERAPY)

The main stay of pharmacological treatment of acute OP poisoning is co-administration of atropine and oximes.

- i) **Anticholinergic drugs**: They are the main stay of treatment and should be given as soon as the airway has been maintained, *atropine* is given initially mg/I/V bolus doses and then at doses of 2-5 mg I/V bolus every 5-15 minute until signs of atropinization appear. Atropine effectively ameliorates the muscarinic hyperactivity, prevents pulmonary edema and excessive secretions. It should be continued for 4-7 days depending upon the severity of poisoning as atropine crosses the blood brain barrier so over dosage (toxicity) occurs in the form of delirium, hallucinations, confusion, fever and tachycardia. Alternative to atropine, glycopyrrolate – a quaternary ammonia compound does not cross the blood brain barrier and so gives better control of secretions and less tachycardia⁴¹. The maximum total dose in OP poisoning is 140-167 mg⁴³.
- ii) **Oximes**: They are nucleophilic agents which reactive phosphorylated acetylcholinesterase by binding to organophosphorus molecule⁴⁴. They are (a) pralidoxime methylsulphate (b) obidoxime (c) H 16 (d) HL07(e) B169f) TMB4 (trimedoxime). All these are not considered as universal reactivators; the use of oximes in acute OP poisoning has been derived from early observations of their protective effect in experimental nerve gas poisoning⁴⁵. Regarding the continuation of oxime therapy and their dosages in acute OP poisoning, electrophysiological studies have documented the decrement response to high frequency 30 Hz RNS (repetitive nerve stimulation), which is an electro diagnostic marker for the intermediate poisoning³⁶.

Pralidoxime iodide – It is water insoluble and given only I/v. It contains

82 mg/ml sol, so large volumes are required for administrations. High doses and repeat administration can cause iodism.

Pralidoxime chloride – It is water soluble and can be given I/v, I/M as well as orally. It contains 640 mg/ml; so small volumes are required for administration. The oral form of the compound was used in Gulf war as a preventive measure in the event of a nerve gas exposure.

Pralidoxime methylsulphate or methanansulphate – It is given I/M
Obidoxime – This drug is available for use in Europe. However, even with dimethyl compounds such as oxymedon, obidoxime are ineffective after 24 hours. However, high and prolonged doses lead to liver toxicity. This drug is available for use in Europe. However, even with dimethyl compounds such as oxymedon, obidoxime is ineffective after 24 hours; high and prolonged doses lead to liver toxicity.

The use of pralidoxime in acute OP poisoning is controversial¹⁴⁶. A recent large, randomized clinical trial compared the use of a single dose of pralidoxime (i.e. 1 gm single bolus dose) with a continuous infusion of 12 grams/day for 3 days, outcome was similar.

Ventilatory support

Mechanical ventilation is needed for several days when respiration is markedly depressed or when chest infection or aspiration of secretions is present. A case series involving 16 patients with continuous infusion of pralidoxime, atropine and ventilatory support has reported mortality as 12.5%.

Role of High dose methyl prednisolone: It has been shown to be beneficial in Type-III paralysis in animal studies^{54,57}.

Role of intravenous diazepam: It is often used to treat marked agitation and seizures in acute OP poisoning. A new drug, Gacyclidine (GK 11) has been shown to ameliorate CNS toxicity.

CONCLUSION

OP compounds are the most widely used toxic agent, for suicidal poisoning in developing countries; accidental poisoning occurs in workers engaged in spraying operations. They irreversibly phosphorylate cholinesterase leading to the accumulation of acetylcholine at the cholinergic nerve endings such as autonomic ganglia, parasympathetic nerve endings and motor end plates. Regulations controlling their use and storage must be made by Govt. of India and this is the need of the hour.

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