

MANAGEMENT OF ORGANOPHOSPHORUS POISONING

Dr Sumati Joshi, Assistant Professor; Dr. Binaya Biswas, Assistant Professor, Department of Anaesthesiology and Critical Care Medicine; Dr. Gyanendra Malla, Senior Resident, Department of Family Medicine, B.P.Koirala Institute of Health Sciences, Dharan, Nepal. Address for correspondence: Dr Sumati Joshi; e mail: gs_malla@yahoo.com

Organophosphorus compounds are chemical agents in widespread use throughout the world, mainly in agriculture. They are also used as nerve agents in chemical warfare (e.g. Sarin gas), and as therapeutic agents, such as ecothiopate used in the treatment of glaucoma. They comprise the ester, amide or thiol derivatives of phosphoric acid and are most commonly used as pesticides in commercial agriculture, field sprays and as household chemicals. Organophosphates are of significant importance due to their practical usefulness and chemical instability. This instability means a lack of persistence in their surroundings.

There are no rules and regulations governing the purchase of these products, and they are therefore readily available "over the counter", despite them being a major cause of morbidity and mortality. Exposure to organophosphates in an attempt to commit suicide is a key problem, particularly in the developing countries, and is a more common cause of poisoning than the chronic exposure experienced by farmers or sprayers in contact with pesticides. Estimates from the WHO indicate that each year, 1 million accidental poisonings and 2 million suicide attempts involving pesticides occur worldwide. Intoxication occurs following absorption through the skin, ingestion via the GI tract or inhalation through the respiratory tract. Early diagnosis and prompt treatment is required to save the patient's life.

Classification:

There are more than a hundred organophosphorus compounds in common use. These are classified according to their toxicity and clinical use:

1. Highly toxic organophosphates: (e.g. tetra-ethyl pyrophosphates, parathion). These are mainly used as agricultural insecticides.
2. Intermediately toxic organophosphates: (e.g. coumaphos, clorpyrifos, trichlorfon). These are used as animal insecticides.
3. Low toxicity: (e.g. diazinon, malathion, dichlorvos). These are used for household application and as field sprays.

Mechanism of Action of Organophosphorus Compounds

Acetylcholine (ACh) is the neurotransmitter released at all postganglionic parasympathetic nerve endings and at the synapses of both sympathetic and parasympathetic ganglia. It is also released at the skeletal muscle myoneural junction, and serves as a neurotransmitter in the central nervous system.² ACh is hydrolyzed by acetylcholinesterase into two fragments: acetic acid and choline.

Acetylcholinesterase is present in two forms: True acetylcholinesterase which is found primarily in the tissues and

erythrocytes, and pseudocholinesterase which is found in the serum and liver.

Organophosphorus compounds are acid-transferring inhibitors of cholinesterase. They cause cholinesterase to become firmly (and sometimes irreversibly) phosphorylated. This means that the action of cholinesterase will be inhibited. Cleavage of the carbon-enzyme bond from ACh is complete in a few microseconds. However, the breaking of the phosphorus-enzyme bond requires a period varying from 60 minutes to several weeks, depending on the organophosphorus compound involved.

Reactivation of the inhibited enzyme may occur spontaneously. The rate of reactivation will depend on the species, the tissue, and the chemical group attached to the enzyme. Reactivation may be enhanced by hydrolysis of the acid-radical-enzyme through the use of oximes (i.e. reactivating agents). Response to reactivating agent's declines with time; this process being caused by "ageing" of the inhibited enzyme. Ageing is probably the result of the loss of one alkyl or alkoxy group, leaving a much more stable acetylcholinesterase.³ The aged phosphorylated enzyme cannot be reactivated by oximes.⁴

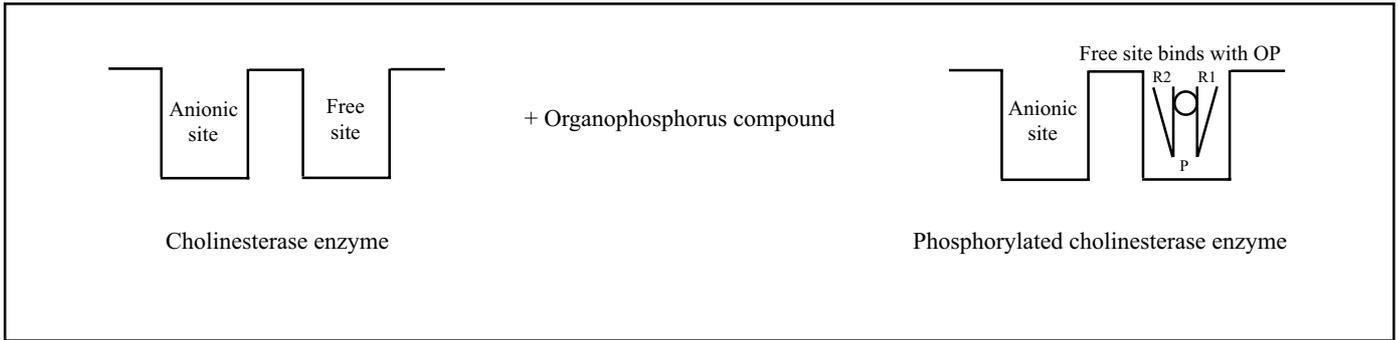
Accumulation of acetylcholine causes overstimulation of both muscarinic and nicotinic receptors, and subsequently disrupts the transmission of nerve impulses in both the peripheral and central nervous system.

Pharmacokinetics

Most organophosphates are highly lipid soluble compounds and are well absorbed from intact skin, oral mucous membranes, conjunctiva and the gastrointestinal and respiratory tracts. They are rapidly redistributed to all body tissues. The highest concentrations are found in the liver and kidneys. This high lipid solubility means that they easily cross the blood/brain barrier and therefore produce potent effects on the CNS. Metabolism occurs principally by oxidation in the liver with conjugation and esterase hydrolysis producing a half-life of minutes - hours. The oxidative metabolites of malathion and parathion (malaoxon and paraoxon) are active forms and are subsequently hydrolyzed into inactive metabolites. Elimination of organophosphorus compounds and its metabolites occur mainly via urine, bile and faeces.

Clinical features of Organophosphorus Poisoning

Following exposure to organophosphorus compounds, the toxic features are usually obvious within 30 minutes to 3 hours. This may be delayed in some cases depending on the rate and amount of systemic absorption. The majority of patients give a history of intentional or accidental ingestion of organophosphorus compounds. Toxicity is produced by the rapid absorption of the compound through the gastrointestinal, respiratory tracts and skin.



The clinical symptoms and signs are non-specific and will depend on the specific agent, the quantity and the route of entry. Some patients present with vomiting, diarrhoea and abdominal pain, whilst others may be unconscious on arrival at the hospital. A high index of suspicion is therefore needed to make an early diagnosis. The clinical features can be broadly classified as secondary to the (a) muscarinic effects (b) nicotinic effects and (c) central receptor stimulation.⁵ Early cases present predominantly with parasympathetic over-activity, and a characteristic garlic smell. The end result may be a multi-system manifestation involving the gastrointestinal, respiratory, cardiovascular and nervous systems, as well as involvement of skeletal muscle, other organs and metabolic effects such as hypo- or hyperglycemia. Most fatalities occur within 24 hours and those who recover usually do so within 10 days.

Cardiac manifestations

The commonest cardiac manifestations following poisoning are hypotension (with warm, dilated peripheries), and bradycardia. Patients seldom present with tachycardia and hypertension due to predominant nicotinic receptor blockade. Cardiac manifestations are often the cause of serious complications and fatality. Electrocardiographic manifestations include prolonged Q-Tc intervals, elevation of the ST segment, inverted T waves and a prolonged PR interval. There may also be rhythm abnormalities such as sinus bradycardia, ventricular extrasystoles, ventricular tachycardia and fibrillation. Ludomirsky et al 6 described three phases of cardiac toxicity following organophosphate poisoning:

- **Phase I:** A brief period of increased sympathetic tone

Table 1. Symptoms and signs of organophosphorus poisoning		
Muscarinic receptors	Nicotinic receptors	Central receptors
<p>Cardiovascular</p> <ul style="list-style-type: none"> ● Bradycardia ● Hypotension <p>Respiratory</p> <ul style="list-style-type: none"> ● Rhinorrhoea ● Bronchorrhoea ● Bronchospasm ● Cough <p>Gastrointestinal</p> <ul style="list-style-type: none"> ● Nausea/vomiting ● Increased salivation ● Abdominal cramps ● Diarrhoea ● Faecal incontinence <p>Genitourinary</p> <ul style="list-style-type: none"> ● Urinary continence <p>Eyes</p> <ul style="list-style-type: none"> ● Blurred vision ● Increased lacrimation ● Miosis <p>Glands</p> <ul style="list-style-type: none"> ● Excessive salivation 	<p>Cardiovascular</p> <ul style="list-style-type: none"> ● Tachycardia ● Hypertension <p>Musculoskeletal</p> <ul style="list-style-type: none"> ● Weakness ● Fasciculations ● Cramps ● Paralysis 	<p>General effects</p> <ul style="list-style-type: none"> ● Anxiety ● Restlessness ● Ataxia ● Convulsions ● Insomnia ● Dysarthria ● Tremors ● Coma ● Absent reflexes ● Respiratory depression ● Circulatory collapse

- **Phase II:** A prolonged period of parasympathetic activity including AV node blockade
- **Phase III:** Q-T prolongation followed by torsade de pointes, ventricular tachycardia and ventricular fibrillation.

The mechanism of cardiac toxicity is unclear and the following have all been postulated:

- A direct toxic effect on the myocardium
- Overactivity of cholinergic or nicotinic receptors causing haemodynamic alteration
- Hypoxia
- Acidosis
- Electrolyte abnormalities
- High dose atropine therapy (used as treatment for organophosphate poisoning).

Respiratory manifestations

Respiratory manifestations of acute organophosphorus poisoning include bronchorrhoea, rhinorrhoea, bronchospasm and laryngeal spasm. This is due to the action of the organophosphate on muscarinic receptors. The integrity of the airway may be compromised by excessive secretions. The nicotinic effects lead to weakness and subsequent paralysis of respiratory and oropharyngeal muscles. This increases the likelihood of both airway obstruction and aspiration of gastric contents. Finally, central neurological depression may lead to respiratory arrest.

Gastrointestinal manifestations

Symptoms resembling gastroenteritis such as vomiting, diarrhea and abdominal cramps are the first to occur after oral ingestion of an organophosphorus compound.

Neurological manifestations

A large number of patients, following acute exposure to organophosphorus compounds, will require prolonged ventilatory support in the intensive care unit due to neuromuscular weakness. The neurological manifestations have therefore been a primary focus of interest. There has been an emphasis on reducing the incidence of neuro-muscular respiratory failure. Three different types of paralysis are recognized based largely on the time of occurrence and their differing pathophysiology:

- Type I paralysis or acute paralysis
- Type II paralysis or Intermediate syndrome
- Type III paralysis or Organophosphate- induced delayed polyneuropathy

Type I paralysis or acute paralysis is seen during the initial cholinergic phase. This is when large numbers of both muscarinic and nicotinic receptors are occupied by acetylcholine, leading to persistent depolarization at the neuromuscular junction. Clinical features include muscle fasciculation, cramps, twitching and weakness. At this stage the patient may require ventilatory support due to the weakness of the respiratory muscles leading to respiratory depression and arrest.

Type II paralysis or Intermediate syndrome. This was first described in 1974 by Wadia et al⁷ as type II paralysis and subsequently termed "The Intermediate Syndrome" by Senanayake⁸. This syndrome develops 24-96 hours after the poisoning. Following recovery from the acute cholinergic crisis, and before the expected onset of delayed neuropathy, some patients develop a state of muscle paralysis. The cardinal feature of the syndrome is muscle weakness affecting the proximal limb muscles and neck flexors. There is a relative sparing of the distal muscle group. One of the earliest manifestations in these patients is the inability to lift their head from the pillow (due to a marked weakness in neck flexion). This is a useful test to establish whether or not a patient is likely to develop respiratory muscle weakness. Of the cranial nerves, those supplying the extra-ocular muscles are mostly involved, with a lesser effect on VII and X. This syndrome persists for about 4-18 days and most patients will survive unless infection or cardiac arrhythmias complicate the course.

Type III paralysis or organophosphate- induced delayed polyneuropathy (OPIDP) is a sensory-motor distal axonopathy that usually occurs after ingestion of large doses of an organophosphorus compound.⁹⁻¹¹ The neuropathy presents as weakness and ataxia following a latent period of 2-4 weeks. Initial stimulation causes excitatory fasciculation, which then progresses to an inhibitory paralysis. The cardinal symptoms are distal weakness of the hands and feet. This is often preceded by calf pain, and in some cases, parasthesia of the distal part of the limbs. Delayed CNS signs include tremor, anxiety and coma.

Diagnosis

As there are no clinical features specific to organophosphorus poisoning, diagnosis requires a high index of suspicion. The combination of a history of exposure and the typical clinical features, make the diagnosis of organophosphorus poisoning relatively easy. The history of exposure may be denied by patients who have attempted suicide, or unavailable in unconscious patients. Helpful signs of poisoning include the pungent garlic-like odour of organophosphorus in breath and vomitus, miosis, bradycardia and muscle fasciculations. Excessive salivation, excessive respiratory tract secretions and lacrimation are other helpful signs. It should be remembered that some patients may present with the nicotinic effects of tachycardia, hypertension and mydriasis (rather than the anticipated bradycardia and hypotension).

Treatment is initiated immediately on clinical suspicion, without waiting for blood investigations (although these are important, to confirm the diagnosis, and rule out multiple poisonings and other metabolic causes of an altered neurological state). Both true and pseudocholinesterase levels can be estimated to assess poisoning. These levels are markedly reduced in organophosphorus poisoning. While true cholinesterase correlates with the severity of poisoning at presentation, pseudocholinesterase levels do not. A 25% or greater reduction in true cholinesterase level is indicative of organophosphorus poisoning.

Management

Decontamination

Skin decontamination is very important step that should never be neglected or hurried. The patient should be removed from the site of exposure and their clothes removed. The patient's body should then be thoroughly washed with soap and water to prevent further absorption from the skin. Prior to treating the patient, staff should be protected from the organophosphate by wearing gloves, gowns and eye protectors. Gastric emptying should then be considered if the patient presents within 1 hour of ingestion. Gastric lavage is the only means of emptying the stomach in unconscious patients in which case the airway needs to be protected. The patient should receive activated charcoal 0.5-1 gm/ kg every four hours to promote adsorption in the gastrointestinal tract. Lavage is preferred to enforced emesis as this may precipitate seizures.

Management of Organophosphorus compounds poisoning

- Skin decontamination
- Airway protection if indicated
- Gastric lavage
- Activated charcoal 0.5-1gm/kg every 4hr
- Anticholinesterase: Atropine/glycopyrrolate
- Cholinesterase reactivator: Pralidoxime
- Ventilatory support
- Inotropic support
- Feeding-enteral/parental

Airway and respiration

The airway should be secured and adequate oxygenation ensured. This is important as atropine can precipitate ventricular fibrillation in hypoxic patients. Paradoxically, the early use of adequate atropine will dry respiratory secretions, improve muscle weakness and thereby improve oxygenation. Careful observation of the respiratory status is required as these patients are prone to develop respiratory failure during both the acute phase and the intermediate syndrome. The following should be monitored on a regular basis to assess the patient's respiratory status:

- Respiratory rate
- Tidal volume/ vital capacity
- Neck muscle weakness
- Ocular muscle involvement eg. diplopia
- Arterial blood gas analysis

Cardiac monitoring

As mentioned earlier, a wide range of cardiac manifestations can occur and careful haemodynamic and electrocardiac monitoring should be undertaken in all patients. It should be remembered that hypoxaemia, metabolic and electrolyte abnormalities can all contribute to cardiac arrhythmias. Some arrhythmias may require cardiac pacing.

Anticholinergics

Atropine. Treatment with anticholinergics (to antagonize the muscarinic effects of the organophosphate on the CNS, CVS and gastrointestinal tract), is still the mainstay of treatment, and should be started as soon as the airway is secured. The recommended starting dose of atropine is a 2mg IV bolus. Subsequent doses of 2-5mg every 5-15 minutes should be administered until atropinization is achieved. The signs of adequate atropinization include an increased heart rate (>100 beats/min.), moderately dilated pupils, a reduction in bowel sounds, a dry mouth and a decrease in bronchial secretions. Contrary to earlier belief, total atropinization (fully dilated pupils, absent bowel sounds, heart rate >150 beats/min) is no longer necessary. Satisfactory management involves keeping the patient adequately atropinized without the attendant risks of total atropinization (hyperexcitability, restlessness, hyperpyrexia and cardiac complications). Continuous atropine infusions are used in some centres in doses of 0.02-0.08mg/kg/hr.¹³ The dose of atropine required is maximal on day 1 and tends to decrease over the next few days. Atropine does not reverse the skeletal muscle effects.

Glycopyrrolate. Some studies have shown that glycopyrrolate is equally effective, with fewer central nervous system side effects and a better control of secretions.¹²

Cholinesterase reactivator

Oximes are nucleophilic agents that re-activate the phosphorylated acetylcholinesterase by binding to the organophosphorus molecule. The use of oximes in acute organophosphorus poisoning has been a controversial subject for the last two decades as there have been very few randomized controlled trials that have addressed the role of pralidoxime (PAM).

Pralidoxime has three main actions:

- A direct reaction converting the organophosphate to a harmless compound.
- A transient reaction protecting the enzyme from further inhibition.
- Reactivation of the inhibited alkyl phosphorylated enzyme to free the active unit (if given early enough)

The reactivating action of pralidoxime is most marked at the nicotinic skeletal neuromuscular junction. It does not reverse the muscarinic manifestations of organophosphorus poisoning. Pralidoxime should be started as early as possible to prevent permanent binding of the organophosphate to acetylcholinesterase. Once this has occurred, receptor regeneration is required to allow recovery. The recommended dose of pralidoxime in organophosphorus poisoning is 1 gram, by intravenous injection, every 6-12 hour in adults (maximum dose 12g/24 hours) and 25-50mg/kg in children. Pralidoxime should be continued until adequate spontaneous ventilation is achieved by the patient. The effective plasma concentration is 4mg/litre and the patient should show signs of improvement 10-40 minutes after its administration. Plasma and pseudocholinesterase levels should ideally be monitored during treatment. Side effects of pralidoxime include drowsiness, visual

disturbances, nausea, tachycardia and muscle weakness, so treatment should be reserved for potentially fatal cases.

Case Insert:

A 20 year old female was brought to the casualty department one hour following the ingestion of an organophosphorus compound.

On arrival, the patient was drowsy with a garlic-like odour from the frothy secretions in her mouth. She had a heart rate of 60 beats/minute, blood pressure of 100/60mmHg and constricted pupils. In order to protect the airway, the trachea was intubated immediately after securing intravenous access. Gastric lavage was performed with normal saline and 50gm of activated charcoal introduced via the Ryle's tube. Atropine 2mg was administered intravenously and repeated every 5 minutes until the pupils dilated, HR increased to >100beats/minute and secretions from the endotracheal tube decreased. Pralidoxime 1gm was slowly given intravenously. The patient was then transferred to the ICU for ventilatory support and close monitoring.

In the intensive care unit, the patient was sedated with midazolam 1mg/hr and ventilatory support continued. An atropine infusion was started at 4mg/hour but due to copious secretions from both mouth and respiratory tract was increased to 6-8mg/hour. This was gradually reduced and finally stopped on day 10 of her stay in ICU. Pralidoxime 1gm IV was repeated 6 hourly for a week. Her condition deteriorated with the development of pneumonia, which was successfully treated with appropriate antibiotics. A percutaneous dilatational tracheostomy was performed on the 12th day of her ICU stay. weaning from ventilatory support proved difficult due to her pneumonia but on the 17th day after admission, the patient was discharged from ICU to the general ward.

Prevention

Improved regulation of the availability of pesticides, strict regulation of vendors, and modifications in packaging of pesticides may all help reduce the use of organophosphates as poisons. Adequate provision of information to the public, regular training of health care providers, better availability of drugs / antidotes and the establishment of poison information centres will facilitate in reducing the morbidity and mortality related to organophosphorus poisoning. Insecticides should be kept out of reach of children, to prevent accidental poisoning. During agricultural spraying, proper precautions should be taken to prevent inhalation and accidental ingestion of the substance.

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Further Reading

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