Organophosphate poisoning : A review

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Abstrak

Pestisida organofosfat digunakan secara luas di seluruh dunia. Keracunan oleh bahan ini merupakan masalah kesehatan masyarakat, terutama di negara berkembang. Zat neurotoksik organofosfat merupakan bahan yang dianggap mengancam dalam bidang militer dan terorisme. Mekanisme toksisitas bahan ini adalah dengan cara menghambat asetilkolinesterase yang mengakibatkan menumpuknya neurotransmitor asetilkolin dan terjadi rangsangan terus-menerus pada reseptor asetilkolin pada sistem saraf sentral maupun perifer. Selain krisis kolinergik, organofosfat dapat menimbulkan berbagai sindrom neurologis, baik akut maupun kronik. Sedangkan gejala peralihan (intermediate) terjadi 1-4 hari setelah krisis kolinergik teratasi. Pengobatan standar terdiri dari reaktivasi asetilkolinesterase dengan antidot golongan oksim (prolidoksim, oksidoksime, HI-6 dan HLo7), dan pengendalian efek biokimia asetilkolin dengan menggunakan atropin. Golongan oksim yang baru HI-6 dan Hlo7 merupakan reaktivator asetilkolinesterase yang lebih cocok dan efektif untuk keracunan akut dan berat dibandingkan dengan prolidoksim dan obidoksim. Penderita yang mendapat pengobatan segera, biasanya dapat sembuh dari toksisitas akut, namun gejala neurologis ikutan dapat saja terjadi. ***(Med J Indones 2003; 12: 120-6)***

Abstract

Organophosphate pesticides are used extensively worldwide, and poisoning by these agents, particularly in developing nations is a public health problem. Organophosphorous nerve agents are still considered as potential threat in both military or terrorism situations. The mechanism of toxicity is the inhibition of acetylcholinesterase, resulting in accumulation of the neurotransmitter acetylcholine and continued stimulation of acetylcholine receptors both in central and peripheral nervous systems. Beside acute cholinergic crisis, organophosphates are capable of producing several subacute or chronic neurological syndromes. The well described intermediate syndrome (IMS) emerges 1-4 days after an apparently well treated cholinergic crisis. The standard treatment consists of reactivation of inhibited acetylcholinesterase with an oxime antidote (pralidoxime, obidoxime, HI-6 and Hlo7) and reversal of the biochemical effects of acetylcholine with atropine. The newer oximes HI-6 and Hlo& are much more suitable and efficacious acetylcholinesterase reactivator for severe acute nerve agent induced poisoning than currently used pralidoxime or obidoxime. Patients who receive treatment promptly usually recover from acute toxicity but may suffer from neurologic sequelae. ***(Med J Indones 2003; 12: 120-6)***

Keywords*: poisoning, insecticide, organophosphate (OP), carbamates, acetylcholinesterase, oxime, pralidoxime, obidoxime, HI-6, HLo7*

Organophosphates (OP) were introduced in 1854 but their toxicity was not known till 1931. The first organophosphate insecticide was tetraethyl pyrophosphate (TEPP). It was developed in Germany as a substitute for nicotine, which was in short supply in that country during Second World War. Related extremely toxic compounds such as Tabun and Sarin were kept secret as nerve gas chemical warfare agents. Since Schrader synthesized parathion in 1944, organophosphate compounds have developed into largest and most versatile group of pesticides in use today.[1] Parathion has the dubious distinction of being the pesticide most frequently involved in fatal poisoning. Insecticides have most frequently been involved in human poisonings and organophosphate compounds have most frequent been offending agent.

In India organophosphates as pesticides were introduced in 1960's and toxicity was first reported in 1962.[2] Organophosphate compounds have undoubtedly contributed to increased yield of agricultural products and also in containment of vectors of certain illnesses like malaria. Unfortunately they are also an important cause of suicidal or accidental poisoning. Organophosphate compounds that are widely used in farming in the form of plant protecting preparations, are strong poisons and a source of poisoning. It is much more common in underdeveloped countries then in developed countries and complete understanding of it is essential for the emergency physicians.

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Organophosphate compounds are associated with important public health problem. Suicidal attempts apart, with increasing use of pesticides in agriculture, the agricultural worker as well as those involved in manufacturing are at increasing risk of poisoning. Rarely they may be used in homicidal poisoning. The use of organophosphate compounds as nerve gas agents have been banned by the Geneva Convention in 1974 as a part of larger ban on chemical warfare. Nevertheless, their sporadic use in warfare and terrorist crimes is still continuing. Exposure to OP based nerve gas agents was implicated as a major etiological factor for "Gulf War syndrome" observed in the Gulf war veterans.

CLASSIFICATION

Pesticides are chemicals or mixtures of chemicals, which are used for destroying, repelling, mitigating or reducing pests. Modern pesticides are in general, organic chemicals i.e. compounds which contain carbon. The organic pesticides are further subdivided into organophosphates, carbamates, organochlorines, organomercurials, thiocarbamates, ureas etc. Common organophosphate and carbamate insecticides are given in Table 1.

Table 1. Some available organophosphate and carbamate insecticides

Organophosphate insecticides :

Abate, azinophos-methyle (Guthion), carbophenothion (Trithion), chlorthion, ciodrin, coumaphos, DEF, dementon (Systox), diazinon (Basudin), dicaothon (Di-Captan), dichlorovas (Nuvon), dicrptophos (Bidrin), dimethoate (Cygon), dioxathion (Delnav), disulfoton (Disyston), echothiophate (Phospholine), EPN, ethion (Nialate), fenthion (Baytex), malathion (Malathion, Cythion), menazon, merphos, methyl demeton (Metasystox), methylparathion (Metacid), methyltrithion, mevinphos (Phosdrin), monocrotophos (Azodrin), mipafox, naled (Dibrom), paraoxon (mintacol), parathion, phosphamidon (Dimecron), phorate (Thimet), runnel (Korlan), schradan (Sytam, Pestox), TEPP (Baladan, Tetron), trichlorfon (Dipterex, Tugon), chlorpyrifos (Dursban, Lorsban)

Carbamate insecticides :

Aldicarb (Temik), aminocarb (Matacil), bendocarb (Ficam), propoxur (Baygon), Bux, cabaryl (Sevin), carbofuran (Furaxdan), dimetan, dimetilan, dioxacarb, fenethcarb, foremetanate, landrin, meobal, methomyl Ilannate, Nudrin), mexacarbate (Zectran), tripate, tsumacide

MECHANISM OF ACTION

Organophosphates by irreversibly inhibiting carboxylic esterase enzyme, true cholinesterase and pseudo-cholinesterase, result in accumulation of acetycholine at muscarinic, nicotinic, and central nervous system synapses.

True cholinesterase is chemically acetylcholinesterase (AchE) and is present in the grey matter of central nervous system, sympathetic ganglion, myoneural junctions and erythrocytes. Pseudocholinesterase in chemically butyrylcholinesterase and is present in white matter of central nervous system, plasma, pancrease, liver and intestinal mucosa. The inactivation of acetylcholine occurs by binding at two different sites on cholinesterase enzyme. Anionic site of cholinesterase enzyme binds with quaternary nitrogen atom of acetylcholine and esteratic site binds with the carboxyl group of acetylcholine. This results in formation of acetylcholine-cholinesterase complex. There is release of choline and cholinesterase is acetylated, the later is regenerated. The turning over time of acetylcholinesterase is very short. After OP poisoning the phosphate radical of organophosphate compound binds firmly to the active (esteratic) site of the acetylcholinesterase, resulting in the formation of inactive phosphorylated enzyme. In the absence of acetylcholinesterase, there is continuous and prolonged excess of acetylcholine in the autonomic, neuromuscular and central nervous system synapes, hence the various clinical manifestations. Hydrolysis of this inactive phosphorylated enzyme is a slow process, which may take days to weeks before new cholinesterase is synthesised, if not treated. Rapid reactivation is possible with help of pharmacological agents like oximes. Finkelstein et al.[3] reported after studying acetylcholinesterase activity in brains of poisoning victims, that acetylcholinesterase inhibition was regionally selective. The most significant decreases were observed in the neo-cerebellum, thalamic nuclei and the cortex. The exact mechanism how organophosphate affect central nervous system is unclear. There is another esterase in the brain and spinal cord called neurotoxic esterase (NTE). Organophosphates cause phosphorylation of the NTE. Depressed levels of this enzyme are believed to lead to delayed neurotoxicity.[4] A high level of inhibition (70%-80%) of NTE is possibly necessary for the neurotoxicity. Next step is "aging" of the phosphorylated enzyme complex. Compounds that do not "age" do not cause polyneuropathy. The amount and type of organophosphate consumed determine the development of the polyneuropathy.[5,6]

Carbamates are rapidly reversible inhibitors of cholinesterase, so oximes are contraindicated for the treatment of carbamate poisoning.

METABOLISM

Organophosphates are absorbed through the skin, lung and gastrointestinal tract. They are widely distributed in human body including brain and adipose tissue, because they are lipid soluble. They are slowly eliminated by hepatic metabolism. Oxidative metabolites are active, but subsequent hydrolysis produces inactive metabolites.

Carbamates are rapidly eliminated by serum cholinesterases and by hepatic metabolism.

Clinical manifestations

Organophosphate and carbamate compounds produce local, systemic as well as neurological manifestations (Table 2).

Table 2. Signs and symptoms of organophosphate poisoning

Muscranic manifestations :	
Bronchial tree	Bronchoconstriction, increased bronchial secretions, dyspnoea, cyanosis, pulmonary edema
Gastrointestinal	Anorexia, nausea, vomiting, cramps, diarrohea, fecal incontinence, tenesmus
Sweat glands	Increased sweating
Salivary glands	Increased salivation
Lacrimal glands	Increased lacrimation
Cardiovascular	Bradycardia, hypotension
Pupils	Miosis, occasionally unequal
Ciliary body	Blurred vision
Bladder	Urinary incontinence
Nicotinic manifestations :	
Striated muscle	Muscular fasciculations, cramps, weakness, Areflexia, muscle paralysis
Sympathetic ganglia	Hypertension, tachycardia, pallor, mydriasis
CNS manifestations :	
Early	Restlessness, emotional lability, headache, tremor, drowsiness, confusion, slurred speech, ataxia, generalized weakness, coma, convulsions, depression of respiratory and cardiovascular centers.
Intermediate	Ptosis, diplopia, facial palsy, paralysis of ocular, bulbar, neck, proximal and respiratory muscles, absent deep tendon reflexes.
Delayed	Delayed motor/sensory polyneuropathy, Landry Guillain Barre syndrome (rare), pyramidal tract generation.

Local manifestations

Depend on the type of exposure. Exposure to vapors, dust or aerosol can exert local effects on smooth muscles of eyes and respiratory tract resulting in early miosis and blurred vision due to spasm of accomodation. Local effects of skin exposure include localised sweating and fasciculations at the site of the contract. Nausea and vomiting in the beginning are due to taste and smell of organophosphate compounds but later on they are due to muscarinic effects. Carbamates have low dermal toxicity, however aldicarb is extremely toxic by both oral and dermal routes.

Systemic manifestations

Onset of symptoms after exposure to organophosphate compounds is usually rapid, with in a few minutes to two to three hours of exposure. Duration of symptoms is generally from one to five days. There may be wide variability in rate of onset, duration and severity of signs and symptoms in organophosphate poisoning due to market difference in the rate of bio-transformation, distribution and affinity of various OP compounds for acetylcholinesterase. OP compounds and carbamates produce muscarinic, nicotinic and CNS effects.

Muscarinic receptors for acetylcholine are found primarily in bronchial tree, smooth muscles, heart, exocrine glands and pupils. Muscarinic effects includes increased bronchial secretions, broncho-constriction, cough, dyspnoea, tightness in the chest, sweating, increased salivation and increased lacrimation. Increased gastrointestinal tone and peristalsis lead to nausea, vomiting, adominal cramps and involuntary defecation. Urination occurs due to contraction of smooth muscles of bladder. Miosis is common due to constriction of pupils and blurring of vision may occur. In severe poisoning bradycardia, conduction blocks, hypotension and pulmonary edema may occur.

Nicotinic effects occur due to accumulation of acetylcholine at the ending of motor nerves to skeletal muscles and autonomic ganglia. Nicotinic signs include twitching, fasciculation, easy fatigue, cramps, hypertension, tachycardia and in severe cases hyperventilation with respiratory failure can occur. Renal manifestations are rare and manifest as toxic nephritis, though oliguria secondary to hypotension occurs much more commonly.

Neurological manifestations

These may be divided into early, intermediate and delayed or late manifestations.

Early manifestations: These are restlessness, anxiety, headache, giddiness, confusion, tremors, weakness, slurred speech, ataxia, convulsions and coma.

Intermediate manifestations: In 1974 Wadia et al.[7] described the neurological features of organophosphate poisoning into Type I being present at admission to hospital or soon after ingestion of organophosphate compounds and Type II appearing subsequent to admission.

Type II paralysis is same as Intermediate syndrome (IMS) described by Senanayake and Karalliedde in 1987 from Sri Lanka.[6] IMS occurred mainly in severe OP poisoning patients who recover from the acute cholinergic crisis at 7-72 hrs after the onset of acute poisoning. Muscular weakness appears in the following three categories of muscles: (1) neck flexors and proximal limb muscles; (2) muscles innervated by motor cranial nerves and/or (3) repiratory muscles. Intermediate syndrome is characterised by the inability to lift neck due to weakness of neck muscles, lower motor cranial nerves involvement, weakness of eye muscles, facial palsy and proximal muscle weakness. Respiratory insufficiency may be marked requiring ventilatory support. Deep tendon reflexes are usually absent. EMG studies suggest a post synaptic defect.[6] Mild IMS recovers within 2-7 days and has as favorable prognosis. Severe IMS patients with respiratory paralysis needs immediate endotracheal intubation and mechanical ventilation. Recovery of weakness of the respiratory muscles and proximal limb muscles takes longertime.

Delayed manifestations: Appears 9-20 days after ingestion of organophosphate compounds and both central and peripheral nervous systems may be involved. A delayed distal motor-sensory polyneuropathy may occur 2-4 weeks after poisoning by a very limited number of OP agents. Landry Guillain Barre syndrome occurring due to organophosphate poisoning has been described by few authors.[8,9] However, others doubt it's association with organophosphate poisoning.[10] Several cases also show degeneration of pyramidal tracts and when signs of neuropathy are abating bilateral pyramidal signs appear.[4]

INVESTIGATION

In acute poisoning, cholinesterase activity in plasma and in red blood cells in reduced to less than 50% of normal. The normal value of pseudocholinesterase in serum is 100-250 Units/ml and true cholinesterase in red blood cells in 150-300 units/ml. A reduction in red blood cell cholinesterase activity is more specific but less readily available and some organosphosphates may inhibit only one cholinesterase. Without treatment blood cholinesterase activity returns to normal in 4 to 5 weeks. The practice of measuring of AChE levels in acute poisoning is limited. In employees who have been monitored and for whom baseline AChE levels have been established, a diagnosis of poisoning can be made by comparing post exposure AChE levels with baseline levels. If there is no baseline level recorded, and if the offending chemical is in question, the clinician must base treatment on the clinical signs and symptoms.[11]

ELECTROPHYSIOLOGICAL CHANGES

Electrophysiologic findings during paralysis have been extensively described. Repetitive activity if frequent and nerve conduction velocity and distal latency is normal. Repetitive activity consists of an additional wave in the compound muscle potential on a single nerve stimulus. It disappears on repeated stimulus.[12] A decremental response in seen to high rate repetitive nerve stimulation such as 30 and 50 Hz with only some showing decrement at 3 and 10 Hz.[7]

The organophosphate insecticide also causes ECG changes and various tachyarrhytmias and less frequently bradyarrhythmias are described. In animals they have been shown to alter myocardial forces of contraction.[13] In humans clinically arrhythmias are the most frequent problem and death with arrhythmia has been described.[14]

TREATMENT

General measures

Remove the patient from source of contamination, especially from the site of inhalation exposure. Contaminated clothing should be removed and skin should be washed with plenty of water and alkaline soap, which will not only remove, but also help hydrolise the phosphate ester.

In case of oral ingestion gastric should be done with 1-3% potassium permanganate or 0.5% sodium bicarbonate. Gastric lavage may be helpful even hours

after ingestion. Gastrointestinal decontamination should include activated charcoal.

Atropine

Atropine forms the main stay of treatment of organophosphate and carbamate poisoning. Atropine is given 2 to 4 mg intravenous stat followed by 0.5 to 2 mg every 10-15 min till full atropinisation is achieved. Atropine may be used as continuous infusion. Clinical features of atropinisation are; drying of bronchial and mucus membrane secretions, dilated pupils, tachycardia (to maintain pulse rate between 110-120/min) and raised skin temperature. Pupil size and pulse rate are not adequate end points for full atropinisation.

Atropine is a mscarinic receptor antagonist and is ineffective for nicotinic effects of organophosphates. Atropine has little effect on CNS toxicity of organophosphates. The duration of atropine administration is variable, but on an average it is required for 4 to 7 days. The continuous infusion of high doses of atropine significantly reduces the mortality in organophosphate poisoning as against the conventional intermittent administration of atropine.[15]

Oximes

These are nucleophilic agents which reactivate the phosphorylated acetylcholinesterase enzyme by binding to the organophosphate molecule forming a more soluble complex.[16] This makes the esteratic site free and AChE is regenerated. Oximes are not given in carbamate poisoning because of reversible inhibition of cholinesterase enzymes by carbamates. Commonly used oximes are: Pralidoxime (2-PAM), and Obidoxime. Other newer oximes are TMB4 (Trimedoxime), HI-6, and HLo7.

Pralidoxime

The chemical name of pralidoxime is 2-formyl-1-methylpyridinium. Pralidoxime Chloride (2-PAM) is the most commonly used pralidoxime. Others are pralidoxime iodide and pralidoxime methylsuphonate. The specific activity of the drug resides in the 2-formyl-1-methylpyridinium ion and is independent of the particular salt employed. The chloride is preferred because of physiologic compatibility, excellent water solubility and high potency per gram due to low molecular weight. The principle action is to reactivate cholinesterase (mainly outside the central nervous system). Pralidoxime also slows the process of "ageing" of phosphorylated enzyme. Pralidoxime is most effective if administered immediately after poisoning. Generally, little is accomplished if the drug is given more than 36 hours after termination of exposure. There are no definite dosage recommendations for the use of 2-PAM in the treatment of organophosphate poisoning. Initial dose of 1 to 2 g intravenously preferable as an infusion in 100 ml saline over 15 to 20 minutes. The dose may be repeated every 4 to 6 hours. The minimum therapeutic concentration in plasma is 4 μg/ml; continuous iv infusion (0.5 g/h) maintains pralidoxime levels greater than 4 μg/ml throughout the length of infusion. Considering this continuous I/V infusion of pralidoxime chloride have been recommended as long as reactivation can be expected and until permanent clinical improvement is achieved.[17,18] Some reports advised treatment up to 4-5 days.[19] A recent, large, randomized clinical trial postulated that high dose pralidoxime infusion is no more beneficial in management of OP poisoning than a single 1 g bolus dose.[20] In a retrospective evaluation De Silva et al.[21] raised doubts about usefulness of 2-PAM in organosphosphate poisoning. A major reservation about oxime administration in OP poisoning derives from the knowledge of "ageing" reaction. The aged complex is resistant to reactivation on account of its chemical structure. "Second deterioration" is another clinical phenomenon that limits the beneficial role of oximes. The reason for this phenomenon is not clear. Likely explanation include the release of OP's from fat store to which they are initially distributed and generation of metabolites that also possess AChE properties.

Obidoxime

Obidoxime is the most effective reactivator of human AChE inhibited by pesticides. The added advantage is of obidoxime having the effect on central nervous system also and is quicker in action. Obidoxime is given in the dose of 15 to 30 mg/kg and the added advantage of crossing the blood brain barrier and is quicker in action.

HI-6 and HLo7

The failure of conventional oximes pralidoxime and obidoxime, to reactivate soman inhibited AChE prompted the synthesis of hundreds of oximes with numerous structural modifications. Presently, bispyridinium Hagedorn-oxime HI-6 and HLo7 are regarded the

most promising compound for the treatment of nerve agent poisoning. HI-6 and HLo7 are significantly more effective in reducing mortality than pralidoxime and obidoxime following poisoning with all nerve agents (tabun, Soman and Sarin).[22,23] HI-6 is given in the dose of 15 to 30 mg/kg four times a day. The general improvement of poisoned patients sometimes occur more rapidly than the rise of acetylcholinesterase activity, which points to some direct pharmacological effect of this oxime.[24]

Other pharmacological agents

Centrally acting drugs such as diazepam is used for the treatment of convulsions and is now advised even in the absence of convulsions as it decreases the agitation and other CNS symptoms. Addition of diazepam to the basic antidotal therapy increases the ability of the antidotal therapy to eliminate acute lethal effects of soman.[25] Midazolam has been found to be more effective then diazepam in rats poisoned by toxic organophosphate compounds. Thus suggesting a significant role of gabanergic system in organophosphate poisoning, espcially during the initial stage of intoxication.[26] A new glutomergic antagonist, Gacyclidine (GK 11) has been shown to ameliorate CNS toxicity in OP compounds. It produces prompt reversal of EEG power spectrum and the central respiratory depression in animal experiments. It has not been used in human OP poisoning.[27]

Organophosphates have high lipid solubility so extracorporeal cleaning mechanisms such as hemo-perfusion did not remove any clinically significant amount of organophosphates from the blood of the patients and no change in symptoms occurred.[28]

The logical therapy would be in the form of co-administration of an anticholinergic drug (atropine) and an AChE reactivator (oxime) in order to rapidly obtain the most beneficial effect in the critically ill patient. Seizures that do not respond to specific antidotal therapy, should be treated with intravenous benzodiazepine (diazepam). Artificial respiratory support and other supportive measures are essential for patient survival. They enable the patient to gain necessary time for sufficient recovery of AChE activity.

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