REVIEW ARTICLE

Neurological Syndromes Following Organophosphate Poisoning

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Summary

Organophosphorous compounds, the anticholinesterases, produce significant morbidity and mortality in India. Although exact estimates are not available, hospital based statistics suggest that nearly half of the admissions to emergency with acute poisoning are due to organophosphates. Following accidental or suicidal exposure, these anticholinesterases lead to three well defined neurological syndromes i.e. initial life threatening acute cholinergic crisis which often requires management in intensive care unit, intermediate syndrome in which cranial nerve palsies, proximal muscle weakness and respiratory muscle weakness are common and patients often require respiratory support and delayed organophosphate induced polyneuropathy. In addition to these three classical neurological syndromes following acute exposure and in some following low dose chronic exposure, several neurobehavioural changes have been observed and these have been termed together as 'chronic organophosphate induced neuropsychiatric disoders' (COPIND). Organo-phosphate compounds produce significant pesticide related illness in developing countries. There is, thus, a need to determine exact extent of the problem and to develop appropriate strategies to manage these cases with available resources in these countries.

Key words : Organophosphorous compounds, Poisoning, Neurological syndromes.

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Introduction

Acute organophosphate (OP) poisoning is a significant cause of morbidity and mortality in developing countries including India. Although no exact estimates are available from India, hospital based studies suggest that it is the commonest poisoning in India with nearly half of the admissions to the 'emergency' with poisoning being due to these compounds. Most of these poisonings are usually with a suicidal intent.[1-4] According to WHO, one million serious accidental and two million suicidal poisonings due to insecticides occur worldwide, every year, of which 200,000 die and most of these deaths occur in developing countries.[5] The anticholinesterase organophosphate compounds (OPC) are the organic derivatives of phosphorous containing acids. In India they are freely available in shops and are widely used as insecticides in agriculture and in homes. The phosphonates i.e. organic derivatives of phosphoric acid are not used as insecticides but are used as chemical warfare agents and are not the subject of this review.

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OPCs cause toxicity after their absorption from skin, mucous membranes and respiratory tract following accidental exposure, or from gastrointestinal tract following suicidal ingestion. They are metabolically subjected to hydrolysis by esterases. Although they bind to and interact with a number of enzymes in the human body, yet, it is their action on the enzyme acetylcholinesterase (AChE) that is of clinical importance. These compounds bind to the esteratic site on the acetylcholinesterase molecule phosphorylating the enzyme, leading to inhibition of its normal action.[6] The bond between the esteratic site on the enzyme and the phosphorous atom is stable and takes hours or weeks to break off, depending on the compound involved. Studies have shown that a phenomenon of enzyme ageing occurs which involves cleavage of a radicle from the inhibited enzyme, making it resistant to rephosphorylation. The net result is the accumulation of excess acetylcholine (ACh) at the cholinergic nerve endings all over the body resulting in the characteristic clinical manifestations. Following inhibition, recovery of this enzyme occurs at a rate of about one percent per day.[7] Restoration of AChE occurs by spontaneous rephosphorylation of the enzyme and by new enzyme synthesis. The toxicity of some nerve gases like 'soman' is directly related to the relatively quicker ageing which occurs with these OP compounds.[7]

Following classical OP poisoning, three well defined clinical phases are seen : initial acute cholinergic crisis, the intermediate syndrome and delayed polyneuropathy (OPIDN).[8] In addition, OPs on chronic exposure affect several of the physiological systems which include central nervous system, neuromuscular junctions, cardiovascular system, metabolic and endocrine systems including reproduction. These effects have been reported both in humans and animals.[9]

Acute cholinergic crisis

Organophosphates being inhibitors of esterases particularly the AChE, lead to acute cholinergic crisis in the initial phase. Accumulation of ACh occurs at nerve endings, as AChE is inhibited, leading to initial stimulation and eventually exhaustion of cholinergic synapses. The clinical findings are thereby a mixture of muscrinic effects resulting from the excitation of postganglionic parasympathetic activity, nicotinic effects resulting from accumulation of ACh at neuromuscular junctions and consequent depolarisation and central nervous system effects causing initial excitation and subsequent inhibition of all CNS activity. Actual picture depends upon the balance between the nicotinic and muscrinic stimulation.

The muscrinic symptoms are diarrhoea, lacrimation, salivation, bronchorrhoea, bronchospasm, bradycardia, urination and miosis. However, depending upon the balance between the nicotinic and the muscrinic effects, patient may have hypertension and tachycardia occurring due to nicotinic actions rather than hypotension and bradycardia. The nicotinic receptors activated during acute intoxication lead to muscle paralysis. Fasciculations may be seen and are a reliable sign of poisoning. Progression of paralysis may occur and the muscles of respiration may get affected. The mechanism of action of paralysis is depolarisation and desensitisation blocks induced by acetylcholine at the neuromuscular junctions. Severe intoxication may cause emotional irritability, mental obtundation, cognitive impairment, coma and convulsions because of CNS effects. In the cholinergic phase, paralysis usually passes off within 48-72 hours but complete clinical recovery from all the effects may take up to a week after exposure to these compounds.

Electrophysiological studies done shortly after exposure reveal that single evoked compound muscle action potentials (CMAPS) were followed by repetitive discharges and decrement-increment phenomenon with 10, 20, 50 Hz supramaximal stimulation.[10,11] The repetitive firing following single evoked CMAPS is considered to be due to excessive ACh, in the presence of anticholinesterase, causing antidromic firing due to presynaptic nicotinic receptor stimulation.[12] With the progression of weakness, electromyography shows a decremental response in the motor potentials which, unlike myasthenia, peaks by the second potential. As the degree of muscle weakness progresses, a decremental response in the motor potential can be documented even at slower rates of repetitive stimulation and spontaneous repetitive motor action potentials are absent. A study of single fibre electromyography done in subjects exposed to organophosphorous compounds showed jitter.[13] This phenomenon was postulated to arise from the myoneural junction and depends upon the rise time of the end plate potential. The jitter demonstrates failure of transmission of impulses at the motor end plate and occurs even before the decremental response to tetanic stimulation can be elicited. This abnormality of impulse transmission has been documented to persist long after recovery from the acute cholinergic phase.

Intermediate syndrome

Wadia et al first described this syndrome as type II paralysis.[14] The term intermediate syndrome was however coined by Senanayake and Karalliedde in 1987.[15] The term intermediate syndrome is derived from the fact that it arises between the period of early cholinergic syndrome and the late onset peripheral neuropathy. Its incidence in different studies has been reported to be between 20-68%.[16] This syndrome has been shown to be commonly associated with organophosphorous compunds like diazinon, dimethoate, methylparathion, methamidaphos, monocrotophos, fenthion and ethylparathion. It develops 12-96 hours after exposure and reflects a prolonged action of acetylcholine on the nicotinic receptors and is characterised by muscular weakness in the ocular, neck, bulbar, proximal limb and respiratory muscles. Occasionally, dystonic posturing may be observed and respiratory muscle weakness may be the first clue to the onset of this syndrome. The sensory functions characteristically remain normal and full recovery is evident in 4-18 days. Prolonged suppression of the enzyme acetylcholinesterase is seen during this stage and metabolites of the parent compound may be demonstrable in the urine.

In the first few days of intermediate syndrome, either decrements at low frequencies of stimulation (1 to 3 Hz), with normal series at 10, 20 or 50 Hz, or decrements at intermediate frequencies (10 to 20 Hz), with normal findings at both low and 50 Hz frequencies were recorded.[11] All these abnormalities suggest a post-synaptic defect. Shailesh et al[17] in a study of 214 cases of organophosphorous poisoning, found the incidence of intermediate syndrome to be 18%. Electrophysiological studies done in 21 cases, showed a defect similar to that observed by Senanayake and Karallidde.[15] de-Bleecker et al[18] in a review of 19 cases of intermediate syndrome following organo-phosphorous poisoning found that in the early stages the compound muscle action potential showed a decremental response at low or intermediate frequencies. These decremental responses were maximal at the second response, with a gradual but incomplete recovery by the ninth response. After the first day, either a decremental-incremental response at high frequencies or isolated increments at low frequencies were observed. Normal responses on electromyography were recorded in the days preceding clinical recovery from this syndrome. All these abnormal findings on electromyography suggested a combined presynaptic and postsynaptic defect.

Organophosphate induced delayed polyneuropathy (OPIDN)

OPIDN is common following exposure to OPCs which have weak anticholinesterase activity e.g. triorthocresylphosphate. However, following exposure to the presently available OPCs which have strong anticholinesterase activity, it is distinctly uncommon.[19] In experimental studies involving the hens, a number of OPCs have been found to be neuropathic e.g. mipafox, merphos, leptophos, DEF, EPN, cyanophos and trichloronat.[20,21] However these OPCs are no longer in use. OPIDN sets in after a period of 7-21 days of exposure and causes significant morbidity. The earliest symptoms to be seen are paraesthaesias and calf pain. Weakness initially appears initially in the distal leg muscles causing foot drop, followed by small muscles of the hands. Later it may extend proximally and even involve the truncal muscles. Gait ataxia is disproportionate to the motor and sensory loss. The cranial nerves and the autonomic nervous system are not involved. Deep tendon jerks are absent. The natural history of this neuropathy has revealed that it is subacute in onset in contrast to other toxic axonopathies, with a slow progression over 2 weeks. Clinical involvement of the corticospinal tracts and the dorsal columns becomes apparent when the peripheral neuropathy improves. The prognosis of patients with mild neuropathy is good but those with severe neuropathy are usually left with persistent deficits i.e. claw hand, foot drop, persistent atrophy, spasticity and ataxia.

The occurrence of OPIDN appears to follow the phosphorylation and subsequent ageing of an enzyme in axons called as neuropathy target esterase.[22,23] Although the function of this enzyme is not clear yet it is present in the brain, spinal cord and the peripheral nervous system. Animal experiments have shown that inhibition of the neuropathy-target esterase in the spinal cord produces only a spinal syndrome and not a peripheral neuropathy. For neuropathy to occur, ageing of the enzyme must take place and this involves cleavage of the lateral side chain from the phosphorylated neuropathy-target esterase and occurs in the axon and not the neuron cell body. These molecular events are then followed by characteristic changes in peripheral nerves, including the degeneration of predominantly long axons, with loss of myelin, and Schwan cell proliferation and

macrophage accumulation in nerves. Neuropathy only develops with compounds which are able to inhibit as well as age the neuropathy-target esterase enzyme.

Chronic organophosphate induced neuropsychiatric disorder (COPIND)

Follow-up studies of individuals who have been exposed to high levels of organophosphorous compounds have shown that certain neurobehavioural changes may develop in them, which have been termed together as COPIND.[24] These effects include, drowsiness, confusion, lethargy, anxiety, emotional lability, depression, fatigue and irritability. Many of the studies of long term effects of high-dose organophosphorous compound exposure, are limited by the non-specific nature of these symptoms and by the low sensitivity and specificity of the neuropsychological scoring systems. On the other hand, some of these symptoms could be attributed to the sequelae of convulsions, anoxia, respiratory failure and cardiac arrhythmias that these patients might have suffered during the acute cholinergic syndrome. Savage et al[25] compared 100 matched pairs of individuals with previous organophosphorous poisoning to matched controls, and showed abnormalities in psychometric testing and motor reflexes. Rosenstock et al[26] studied agricultural workers who had a single episode of organophosphorous poisoning two years earlier. They demonstrated impaired neuropsychological testing and problems with visual memory, visuomotor speed, sequencing, problem solving and motor steadiness and dexterity. Chronic neuropsychiatric disorders like anxiety, depression, problems with memory and concentration have been described in workers exposed to organophosphorous compounds. In addition, dystonic reactions, schizophrenia, cog-wheel rigidity, choreoathetosis and electroencephalographical changes have been reported on high-dose exposure. These extrapyramidal symptoms are thought to be due to the inhibition of the acetylcholinesterase in the human extrapyramidal area. Psychosis, delirium, aggression, hallucination and depression, may also be seen during recovery from the cholinergic syndrome. Other types of delayed neurobehavioural effects are seen amongst people exposed to low dose of organophosphorous compounds for prolonged periods. Levin et al[27] found a high level of anxiety in commercial sprayers of insecticides but not in farmers. Behan et al[28] observed that clinical features of psychological syndromes occurring after chronic exposure to organophosphorous compounds had great similarity to chronic fatigue syndrome. A study of electrical activity of the brain of workers exposed to the organophosphorous compound 'sarin', showed that after one year of exposure, there were significant differences, as evidenced by increased beta activity, increased delta and theta slowing, decreased alpha activity and increase in the rapid eye movement during sleep when compared to normal controls. Kelly et al[29] have described a variety of behavioural and electroencephalographic changes in exposed persons. On electrophysiological examination, 'jitter' has been observed in those with chronic long term exposure to organophosphorous compounds. Defects in the perfusion have also been demonstrated using positron emission tomography which persist long after exposure to organophosphorous compounds.[30]

Laboratory Investigations

The most widely used diagnostic tests for OP exposure are the estimation of plasma cholinesterase (PChE) and red blood cell AChE activity.[7] The AChE of RBCs is the same as the one present at target synapses and can be assumed to mirror the effect of OPCs at target synapses. However, between the clinical state and PChE activity and even RBC's AChE activity, no good correlation has been observed, as the acute effects of anticholinesterase depend upon the inhibition of brain and neuromuscular junction AChE and large reserves of these exist at target organs.[31] The usefulness of estimating the cholinesterase activity in OP poisoning is further limited by the variations in the enzyme activity which occurs in the individuals as there exists considerable interindividual variation in the same population[32,33] and can also be affected by disease states. Thus, serial estimations of the enzyme may be more useful. Moreover considerable variation exists between the methods used for estimation and each method has its own range.[34] The methods include electrometric, titrometric and calorimetric assays. Field and fast methods using paper strips are also available.

Treatment

Therapy of the cholinergic phase is with gastrointestinal and skin decontamination and use of atropine as an antidote to counter the muscarinic effects of acetylcholine. Atropinisation, once achieved, should be maintained for 3-5 days, depending upon the compound involved. When muscular paralysis supervenes, mechanical ventilation is required. The initial dose of atropine varies from 2-4 mg intravenously, repeated every 5-15 minutes till full atropinisation is achieved. Atropinisation is

evidenced by pupillary dilation, drying up of secretions and pulse rate > 100. Atropine crosses the blood brain barrier and counters the effect of excess acetylcholine on the extrapyramidal system. Tafuri and Roberts[35] have shown beneficial effects of infusion of atropine 0.02-0.08 mg/kg hourly, on mortality from organophosphorous poisoning when compared to intermittent doses. Adequate oxygenation must be ensured before atropine is used, as animal experiments have shown an increased risk of cardiac arrhythmias when atropine is administered to animals with respiratory failure and hypoxia. Atropine has also been shown to have a salutary effect on neuromuscular transmission by acting on the presynaptic inhibitory muscarinic receptors.[36] Recently a study from China has shown that atropine used in doses smaller than those used traditionally, has a beneficial effect on complication rate of therapy as well as on mortality.[37]

In the cholinergic phase, the use of oximes as rejuvenators of the enzyme cholinesterase has found favour. The beneficial effect of oximes is exerted through the reactivation of enzyme cholinesterase by cleavage of the phosphorylated site and by a direct detoxifying effect on the unbounded organophosphorous compound. Additionally, oximes have an anticholinergic effect when used in normal doses. Therapeutic levels of pralidoxime are reached after 6 hours of intravenous dose of 15-30 mg/kg in man. The recommended dose is 1 gm every 8 hours by intravenous injection. Continues infusions (500 mg/hour) have been advocated by some authors for severe poisoning and have been found to achieve the same therapeutic level as intermittent boluses.[38-40] It is desirable to maintain the therapeutic level of pralidoxime till the enzyme activity has reached maximum and the organophosphorous compound has been eliminated. Toxicity of pralidoxime is evidenced by circumoral paraesthaesias, convulsions, neuromuscular blockade and inhibition of acetylcholinesterase. Studies by Singh et al[41] and DeSilva et al[42] have raised some controversy about the effect of oximes in the management of organophosphorous poisoning. An in-vitro study on human sera by Ganendran et al[43] showed that, pralidoxime did not have any effect on the outcome, when used in organophosphorous poisoning and was associated with the production of potent phosphorylated oximes. On the other hand, Finkelstein et al[44] observed that enzyme reactivation occurs at low serum levels of OP with use of pralidoxime in methyl-parathion and ethyl-parathion poisoning. Experience with obidoxime has shown that with large doses, there is a higher incidence of arrhythmias and impairment of liver functions when used in conjunction with atropine.[45] Another drug that has shown some beneficial effect in organophosphorous poisoning is magnesium. Kiss and Fazekas[46] have reported the control of ventricular premature beats with the use of magnesium in organophosphorous poisoning. In another study, Singh et al[47] observed the reversal of neuro-electrophysiological effect of organophosphorous poisoning with the use of intravenous magnesium sulphate. The actual role of magnesium in the management of organophosphorous poisoning remains to be studied in randomized controlled trials.

Intermediate syndrome is treated by providing respiratory support in the form of mechanical ventilation. The use of atropine is of no clinical significance in intermediate syndrome and full functional recovery of the involved muscle group is the rule. The muscles of respiration are the last to recover and this fact should be borne in mind while weaning the patient from mechanical ventilator.

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