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REVIEW ARTICLE

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ORGANOPHOSPHORUS POISONING

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ABSTRACT

Organophosphate poisoning may cause the life-threatening events resulted in different organs failure. Organophosphorus compounds are extensively used in India as insecticides and most often for suicide purpose. Substantial number of death can be averted by timely treatment and ventilatory support. Organophosphorus (OP) compounds constitute a heterogeneous category of chemicals specifically designed for the control of pests, weeds or plant diseases. Our review article mainly focused on OP poisoning, especially with pesticides, its severity and management of toxic exposure. We conclude that in future, the ministry of agriculture of developing countries, especially India, should concentrate on the optimization and monitoring of usage of OP compounds as pesticides and furthermore, encouraging the farmers to use natural pesticides rather than chemical pesticides .

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KEY WORDS

Organophosphorus compounds, Lactate dehydrogenase, Acetylcholinesterase, Pesticides

INTRODUCTION

Acute organophosphorus poisoning occurs after oral exposure to either low volatility pesticides [e.g. chlorpyrifos, dimethoate] or high volatility nerve gases [e.g. sarin, tabun]. Inhibition of acetylcholinesterase at synapses results in accumulation of acetylcholine and over activation of acetylcholine receptors at the neuromuscular junction and in the autonomic and central nervous systems [1]. In India Organophosphorus poisoning is the most common[2]. Organophosphorus poisoning compounds inhibit acetylcholinesterase at neuromuscular junction, in autonomic and central nervous system resulting in accumulation of acetylcholine [ACh] and over stimulation of ACh receptors resulting in acute cholinergic crisis which is characterized by bradycardia, bronchorrhoea, miosis, sweating, salivation, lacrimation, defecation, urination and hypotension [3].

Organophosphorus [OP] compounds have been widely used for a few decades in agriculture for crop protection and pest control. Thousands of these compounds have been screened and over one hundred of them have been marketed for these purposes. OPs constitute a heterogeneous category of chemicals specifically designed for the control of pests, weeds or plant diseases. Their application is still the most effective and accepted means for the protection of plants from pests, and has contributed significantly to enhance agricultural productivity and crop yields. Some have also been used in the medical treatment of myasthenia gravis, e.g. diisopropyl phosphorofluoridate [DFP], tetraethyl pyrophosphate [TEPP], and octomethyl pyrophosphotetramide [OMPA]. Some OP esters are still used to treat glaucoma [Ecothiopate]. In addition to these beneficial agricultural, veterinary, and medical uses, some highly potent OP anti-cholinesterase compounds, including tabun, sarin and soman, have been used as “nerve gases” in chemical warfare. They are also been used as plasticizers, stabilizers in lubricating and hydraulic oils, flame retardants, and gasoline additives [4].

Pesticides are toxic chemicals by design and their ingestion is a common cause of self poisoning in the developing world. The poisoning due to these chemicals is more often observed with organophosphate [OP] compounds which are easily available and often stored in an improper manner due to lack of awareness of their hazards. There are many such poisoning episodes reported from different parts of the world and also from India. Acute toxicity of OP compounds manifests as a cholinergic crisis and diagnosis is based on the clinical signs and symptoms as well as the measurement of inhibition of erythrocyte [RBC] and/or plasma cholinesterase [ChE] activities. There are reports that pesticide toxicity results suppression of humoral immunity in rodents. However, the information about the influence of pesticides on the human immune system is limited. An increase of activated T-cells has been described in subjects exposed to chlorpyriphos. Since exposure of pesticides in the occupational settings may contribute to modulation of the immune system, the involvement of immune biomarkers in pesticide toxicity studies appears to be of considerable value [5].

Pesticide poisoning from occupational, accidental & intentional exposure is the major health problem in developing world. Millions of people are exposed to danger by hazardous occupational practices and unsafe storage [6].

The organophosphorus compounds are the main weapons against insect pests of

importance in agriculture ,public hygiene and medicine. Since organophosphates are widely used and they are known to pose risks of acute and chronic toxicity to both humans and wildlife ,it is important to monitor exposure to them. Hence it is essential to have detailed study report on the effects [both long term and short term] of organophosphorous exposure in humans. Organophosphorus pesticides [OP] are esters of phosphoric or thiophosphoric acids and are highly toxic to mammals because of their capacity to phosphorylate the active site of actylcholinesterase [AChE], leading to accumulation of actylcholine in synapses. OP has also been described as potent alkylating agents [7].

METABOLISM OF ORGANOPHOSPHORUS COMPOUNDS

ABSORPTION

The degree of absorption depends on the contact time with the skin, the lipophilicity of the agent involved and the presence of solvents, for example xylene, and emulsifiers in the formulation which can facilitate absorption. For powders, the finer the powder the more rapid and complete is skin absorption. Other important factors include volatility of the pesticide [e.g. dichlorvos is much more volatile than Malathion], the permeability of clothing, the extent of coverage of the body surface and personal hygiene. The rate of absorption also varies with the skin region affected. For example, parathion is absorbed more readily through scrotal skin, axillae and skin of the head and neck than it is through the skin of the hands and arms. It is probable that traumatized skin or the presence of dermatitis allows greater absorption of OP compounds. In one study, the mean amount of liquid parathion absorbed dermally was only 1.23% of the measured potential dermal exposure [4].

DISTRIBUTION AND STORAGE:

Following absorption, OP compounds accumulate rapidly in fat, liver, kidneys and salivary glands. The phosphorothioates [P=S], for example diazonin, parathion, and bromophos, are more lipophilic than phosphates [P=O], for example dichlorvos, and are therefore, stored extensively in fat which may account for the prolonged intoxication and clinical relapse after apparent recovery which has been observed in poisoning from these OP insecticides. OP compounds generally are lipophillic and therefore, cross the blood / brain barrier in most cases [4].

BIOTRANSFORMATION:

Phosphates [P=O] are biologically active as acetylcholinesterase [AChE] inhibitors, whereas phosphorothioates [P=S] need bioactivation to their phosphate analogues [oxon] to become biologically active. As a consequence, the features of intoxication after exposure to phosphorothioates [P=S] are delayed unless aerial oxidation has occurred already to generate traces of oxon. OP compounds other than phosphates [P=O] are metabolically activated to their corresponding oxon by oxidation desulfuration mediated by P450 isoforms, by flavincontaining mono-oxygenase enzymes, by N-oxidation and by S-oxidation. The oxons which inhibit AChE can be deactivated by hydrolyses, such as the carboxylases and by A-esterases, for example paraoxonase [4].

ELIMINATION:

Elimination of metabolites occurs mostly in urine with lesser amounts in feces and exhaled air. Some OPs, for example dichlorvos which is not stored in fat to any great extent, may be eliminated in hours whereas the inhibitory oxon of chlorpyrifos or dementon-S-methyl may persist for days because of their extensive storage in fat [4].

DIAGNOSIS OF ORGANOPHOSPHORUS POISONING:

Diagnosis of OP poisoning is based on characteristic clinical features, [miosis is considered to be a very strong indicator of organophosphate poisoning] and history of exposure to a known OP compound. Estimation of serum or RBC cholinesterase level and electro diagnostic tests is helpful in confirming

the diagnosis. Clinical features of OP poisoning appear when RBC cholinesterase activity is <75% of normal and in clinical overt poisoning it is usually <10%. In general, however, serial studies have failed to document a strict relationship between the severity of clinical manifestations and prognosis [4].

PROGNOSIS OF ORGANOPHOSPHORUS POISONING:

There are no validated scoring systems for categorizing severity or predicting outcome of acute organophosphorus poisoning. The highly variable natural history and difficulty in determining the dose and specific organophosphorus compound ingested make predicting outcome for an individual person inaccurate and potentially hazardous, because people admitted in good condition can deteriorate rapidly and require incubation and mechanical ventilation. Prognosis in acute self poisoning is likely to depend on dose and toxicity of the specific organophosphorus compound that has been ingested [e.g. neurotoxicity potential, half life, rate of aging, whether activation to the toxic compound is required [e.g. parathion to paraoxon [pro-poison]], and whether it is dimethylated or diethylated. Prognosis in occupational exposure is better because the dose is normally smaller and the route is dermal [8, 9].

PREVALENCE:

Most cases occur in the developing world as a result of occupational or deliberate exposure to organophosphorus pesticides [10]. Although data are sparse, organophosphorus pesticides seem to be the most important cause of death from deliberate self poisoning worldwide, causing about 200 000 deaths each year [11]. For example, in Sri Lanka, about 10 000-20 000 admissions to hospital for organophosphorus poisoning occur each year. Of these, at least 10% die. In most cases, the poisoning is intentional [12]. Case mortality across the developing world is commonly greater than 20% [11]. In Central America, occupational poisoning is reported to be more common than intentional poisoning, and deaths are fewer [13]. Deaths from organophosphorus nerve gases occurred during the Iran-Iraq war. Military or terrorist action with these chemical weapons remains possible [14].

TOXICOLOGICAL EFFECTS:

Organophosphorus compounds have many toxicological effects on the body.

HEPATOLOGICAL DISORDERS:

Liver is the organ where activation and detoxification of OP compounds takes place. But they are eliminated primarily through kidneys. Earlier the profile of liver marker enzymes, antioxidant enzymes and essential trace elements were found to be adversely affected after OP intoxication to rat. The histopathological changes observed in human liver observed in a forensic laboratory are: Congestion, Centrilobular necrosis, Fatty changes, Alcoholic hepatitis and Sinusoidal dilatation. At high doses of OP, rats exhibitedextreme injury in their liver [4].

NEUROLOGICAL DISORDERS:

Neuronal necrosis has been observed in multiple cortical and subcortical regions in experimental rats exposed to large acute doses of OP compounds. OP also leads to a delay in stimulus classification, which in turn depends on attention resources and the working memory system of the brain, this impairment appears to persist even 6 months after poisoning .Several chronic CNS disturbances due to acute or chronic OP agent. Poisoning has been reported in isolated cases or in worker cohorts. The syndromes vary widely and include parkinsonian and pseudobulbar signs, alterations in effect, libido and memory, psychiatric or more insidious neuropsychological dysfunction and a cerebellar syndrome [4].

RENAL IMPAIRMENT:

Many studies reviewed by the Ontario College show positive association between solid tumours and pesticide exposure, including kidney cancer. Children are constantly exposed to low levels of pesticides in their food and

environment, an elevated risk of kidney cancer was associated with paternal pesticide exposure through agriculture. It has also been reported that the chronic exposure to pesticides leads to kidney failure [4].

EFFECTS ON THE CNS:

Eyer [15] concludes that neuropsychological effects can occur after OP poisoning and that the most frequently reported symptoms include impaired memory and vigilance, reduced information processing and psychomotor speed, memory deficit, linguistic disturbances, depression, anxiety and irritability. There is some concern at present that exposure to OP agents may precipitate psychosis and that chronic psychiatric effects of varying intensity may persist for years. Duffy et al [16] studied the brain electrical activity of workers exposed to the OP compound sarin after a period of 1 year free from exposure. Statistically significant differences from the control group included increased beta activity, increased delta and theta slowing, decreased alpha activity and increased amounts of rapid eye movement [REM] sleep. The findings represented an unexpected persistence of known short-term OP actions and, taken in parallel with the reported long-term behavioral effects, indicate that OP exposure can produce long-term changes in brain function. Perfusion defects, especially in the parietal lobe, have been detected on brain single photon emission computerized tomography [SPECT] after OP poisoning. Acetylcholinesterase, in addition to being an acetylcholine hydrolyzing enzyme, is also a neuromodulator that participates in the phenomenon of neuronal plasticity, i.e. the induction of long-term changes in synaptic function. The loss of this nonenzymatic neuromodulatory role of acetylcholinesterase is considered by some to be the basis for the long-term alterations in cognitive function that may follow long-term occupational exposure to OP compounds [16].

Extra pyramidal manifestations [dystonia, rest tremor, cogwheel rigidity and choreo-athetosis] may occur 4–40 days after OP poisoning. These symptoms may disappear spontaneously in 1–4 weeks in those who survive. This phenomenon has been attributed to the inhibition of acetylcholinesterase in the human extrapyramidal system, which is rich in cholinergic neurons and acetylcholinesterase. Recent studies suggest that Parkinson's disease is more common in patients who report previous exposure to pesticides. The role of glutathione transferases, a ubiquitous group of detoxification enzymes involved in the metabolism of pesticides and other toxins, is probably important in the pathogenesis of pesticide-related disease. Glutathione transferase polymorphisms may influence the body's ability to detoxify pesticides and may increase patients' susceptibility to Parkinson's disease after pesticide exposure [16].

ALTERED IMMUNITY TO INFECTION:

In 1974, Bellin & Chow [17] suggested that OP agents might have an effect on the human immune system. Casale et al [18] demonstrated that parathion suppressed both the primary IgM and IgG response to sheep erythrocytes in inbred and outbred mice. The suppression occurred after a dose that produced cholinergic effects but was absent after a lower dose that did not produce cholinergic effects. Thus, OP-induced immunosuppression was associated with severe cholinergic stimulation, either from a direct action of acetylcholine on the immune system or secondary to the toxic chemical stress associated with cholinergic poisoning. Further work by the same group showed that parathion induced suppression of humoral immunity in mice. A marked impairment of neutrophil chemotaxis stimulated with zymosan-activated serum and a greater frequency of upper respiratory tract infection were demonstrated in workers occupationally exposed to OP pesticides in which a decrease in both serum and red blood cell cholinesterase [acetylcholinesterase] activity was observed. Newcombe [19] showed that patients exposed to OPs developed a number of abnormalities, including an increased incidence of lymphoproliferative disorders associated with impaired natural killer cell and cytotoxic T-cell function. He suggested that these patients

might be prone to persistent viral infections, including Epstein–Barr virus and human herpes virus type 6.

CHANGES IN METABOLISM AND ENDOCRINE ACTIVITY:

In animal experiments, changes in the diurnal pattern of plasma adrenocorticotrophic hormone have been reported following OP insecticide poisoning. Nicotinic receptors also function in brain pathways that increase the release of several pituitary hormones, including vasopressin, adrenocorticotrophic hormone and prolactin. In man, nonketotic hyperglycemia and glycosuria may occur. Significant decreases in serum concentrations of thyroxine and triiodothyronine and an increased secretion of thyroid-stimulating hormone were observed after malathion treatment in rats. Dose-dependent inhibition of phospholipase A_2 by paraoxon has been demonstrated *in vitro*. Hyperamylasaemia and acute pancreatitis have been reported after oral or dermal exposures in man. Dagli & Shaikh [20] found elevated amylase levels in 47% of patients poisoned with Malathion. They found hyperamylasaemia to be closely related to clinical severity and the presence of shock. However, they considered hyperamylasaemia not to be synonymous with acute pancreatitis following OP poisoning. Lipase assay was felt to be indicated for the early diagnosis of acute pancreatitis. It has also been suggested that an elevation of serum amylase on the day of admission is predictive of subsequent respiratory failure [20].

EFFECTS ON ENZYMES AND OTHER METABOLITES:

Organophosphorus agents are known to inhibit other enzyme systems, the consequences of which are as yet unknown. A variety of tissue carboxyesterases abound in serum, liver, intestine and other tissues. However, carboxyesterases may contribute markedly to the metabolic degradation of OP insecticides, such as Malathion, and inhibition of these enzymes may potentiate the toxicity of some OP compounds [21].

Serum lactate dehydrogenase [LDH] activity was significantly elevated in poisoning cases indicating muscle functional impairment due to OP toxicity. LDH activity is directly linked with the glucose metabolism. It is very widely distributed enzyme being found in all organs of our body, but is especially plentiful in cardiac and skeletal muscle, liver, kidney and red blood cells. The CK activity was significantly elevated in poisoning cases and more significant alterations in the patients who died due to poisoning indicating the cardiac functional impairment due to OP poisoning. It is presumed that estimation of CK activity in suspected OP poisoning cases may serve as a corroborative diagnostic parameter, along with alterations in LDH activity when associated with the changes seen in the cholinesterase activity, which is the most important biochemical change seen in OP poisoning cases. An experimental study on rats with soman, an OP, indicated depression in tissues ChE activity accompanied by concurrent increase in serum CPK activity and thus postulating the possible relationship between the different neuromuscular syndromes occurring in the course of an OP poisoning [5].

In sub-set of study population, the serum level of IgG, IgA and circulating immune complexes [C_3 and C_4] in the OP poisoning cases were significantly increased. Exposure to pesticides can cause a number of effects on the immune system varying from a slight modulation of immune functions to the development of clinical immune diseases. Like most other toxic compounds, pesticides are the substances that possess non-protein nature but can combine with protein to form complexes that may be antigenic and cause immunological impairment. Our previous studies on the pesticide formulators exposed to combination of pesticides in industrial settings and pesticide sprayers in field conditions indicated significant positive correlation in serum IgM and serum residue of the pesticide [Hexachlorocyclohexane; HCH] content. The findings may suggest that pesticide induced damage to the immune system may be associated with diverse pathological conditions,

some of which may manifest after a long latency. Moreover, individual differences in endocrine function and nutritional balance, both of which are known to modulate the immune system, are likely to affect susceptibility to pesticide induced immune toxicity. Although the low sample size on the parameters pertaining to immunological profile [IgG, IgA, C_3 and C_4] limits the power to precisely estimate the impairment, however, it may offer some diagnostic value of clinical importance in pesticide poisoning cases [5].

Lohitnavy & Vijayaraghavan [22, 23] recorded that the elevation in serum AST and ALT was due to degeneration and necrosis of liver cells which was accompanied by damage of cell-walls and cytolysis, thereby pouring considerable amount of these mitochondrial enzymes in the blood stream. The heart specific enzyme creatine kinase and CK-MB in the present study were also found to be elevated than that of the controls. The intake of insecticide followed by vomiting causes hypertension and puts excessive stress on heart. This may result in the elevation of CK and CK-MB.

The LDH level in the present study was also found to be elevated in OP consumed patients than that of control individuals. LDH enzyme system plays principal roll in the glycolytic cycle in the cell for conservation of stored energy [i.e. pyruvate or lactate]; this enzyme is released by injury to many different tissues. Serum proteins represent the total amount of proteins including the enzymes and blood proteins. Serum proteins are influenced by a variety of factors such as infection, stress, injury, toxicity, etc. In the present study the level of serum proteins and albumin were found to be significantly reduced. The extent of reduction depends upon the dosage level [7].

The serum glucose levels in the present study were found to be elevated than that of the controls. Attributed the elevation of blood glucose concentration to accumulation of acetylcholine in the adrenals following, inactivation of cholinesterase by the insecticides which stimulate the release of adrenaline into the blood, adrenaline increases cell metabolism; it causes glycogenolysis in the liver and a consequent hyperglycemia as demonstrated in pesticide-exposed animals. Also, an accumulation of acetylcholine in some parts of the brain, e.g., hypothalamus, humoral factors, is released systemically which cause mobilization of peripheral glycogen stores leading to hyperglycemia [7].

The urea and creatinine levels in the present study are elevated in OP consumed patients than that of the controls. AST was found to have its highest concentration in a variety of tissues including liver kidney, brain, skeletal and cardiac muscles. The elevation of this enzyme under the present study also suggests that there is an increased stress on the above said tissues. Hence the urea and creatinine levels under the present study were found to be slightly elevated indicating the stress on kidney due to OP toxicity. Electrolytes are involved in fluid balance of the body. The present study reveals that there was a decrease in the sodium level in the OP consumed patients than that of the controls. Studies reported that low sodium levels are caused by excessive perspiration, intoxication and impairment of adrenal and kidney function. The electrolyte potassium is involved the regulation of cellular fluids. The level of potassium in the present study was found to be slightly elevated than that of the controls. This may be due to the fact that the OP consumption leads to the damage of cells by which the potassium is released out of the cells. Studies also revealed that organophophorous drugs and any other drug which inhibits the activity of acetyl choline esterase causes the elevation of potassium levels in the serum [7].

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