Organophosphorus Insecticide Poisoning

ABSTRACT

Organophosphorus insecticide poisoning is a major global health problem with approximately 3 million poisonings and 200,000 deaths annually. These irreversible inhibitors of acetylcholinesterase produce a well established triphasic effect in man. The initial cholinergic phase due to accumulation of acetylcholine at muscarinic, nicotinic, and central nervous system synapses is a medical emergency that often requires treatment in an intensive care unit. The intermediate syndrome sets in 2-4 days after initial exposure, due to pre- and postsynaptic dysfunction at the neuromuscular junction, and causes respiratory failure for which ventilatory care is necessary. The delayed polyneuropathy sets in about 21 days after exposure, due to phosphorylation of neuropathy target esterase, and produces symmetrical motor weakness of peripheral muscles with a variable sensory component. The organophosphorus compounds are known to produce effects on the nervous, cardiovascular, and reproductive systems in man and animals, producing a wide range of effects. Further interference with temperature regulation, metabolic and endocrine function along with disturbances in vision, affection of vocal cords, and immunity could present challenging medical scenarios for a clinician. Biochemical assays of cholinesterase and organophosphorus agents have undergone considerable review, and progress is being made to develop scientifically reliable criteria for diagnosis and management. Atropine and pralidoximes have been the major therapeutic agents for intoxication, but the unacceptable mortality and morbidity associated with poisoning necessitates change and the use of agents like clonidine and fluoride, which have potentially beneficial effects. There is need for collaborative research and study between the technologically developed countries and the third-world countries, where the vast majority of health disorders associated with organophosphorus insecticides is encountered.

KEY WORDS: PT - prothrombin time; MNPT - mean normal prothrombin time; FNPP - fresh normal plasma pool; INR - International Normalized Ratio.

Pesticides cause approximately 3 million poisonings and 200,000 deaths annually.[1] Organophosphate (OP)-based pesticides are widely used and have emerged as the major contributor to ill health associated with pesticides. These irreversible inhibitors of acetylcholinesterase (AChE) were a leading cause of death in agricultural countries globally.[2] In 1996, the American Association of Poison Control Centers reported 86,914 human exposures to pesticides in the United States.[3] There were 50-70 thousand cases of acute pesticide poisoning reported from 27 provinces of China each year during the 1990s.[4]

Poisoning due to occupational exposure (such as spraying and sheep dips) accounted for about one-fifth of the incidents, with a fatality rate of less than 1%. More than 90% of the nonoccupational incidents were suicidal, with a fatality rate of more than 10%, and the majority of the subjects were young males. Accidental exposure that accounted for 8-10% of incidents and homicidal use (less than 1%) were other forms of poisoning.[5] The reported overall mortality following OPinsecticide poisoning varied from 4-30% in different countries and institutions.[6]

Some OP compounds are well known chemical warfare agents that continue to threaten world peace. OP nerve agents have also been used in subways by terrorist groups and by dictators to suppress communities within countries.

Inhibition of AChE, an enzyme that restricts the activity of acetylcholine (ACh) in space and time, causes an increase in ACh content at sites of cholinergic transmission in the body. At present, the inhibition of AChE is the most plausible explanation for much of the symptomatology following OP intoxication.

Three well defined clinical phases[5]–the initial cholinergic phase, the intermediate syndrome (IMS), and the delayed polyneuropathy (OPIDN)–are known.

Cholinergic phase

The accumulation of ACh at muscarinic sites produces an increase in secretions (bronchorrhea, salivation, tearing, sweating), bronchoconstriction (tightness in the chest, wheezing), bradycardia, vomiting, and an increase in gastrointestinal motility (abdominal tightness and cramps). In the eye, OP agents cause the diagnostic miosis that results in blurring of vision. The effects of increased ACh at nicotinic sites (e.g., the neuromuscular junction) cause muscle fasciculations and a flaccid paralysis due to depolarization block. Inhibition of AChE in the brain leads to headache, insomnia, giddiness, confusion, and drowsiness. Following severe exposure, slurred speech, convulsions, coma, and respiratory depression occur. Death is likely during this initial cholinergic phase due to effects on the heart, respiration, and on the brain. The cholinergic phase usually lasts 24-48 hours and constitutes a medical emergency that requires treatment in an intensive care unit.[5,7]

The intermediate syndrome (IMS)[7]

IMS is characterized by the onset of muscle weakness (of muscles of respiration—the diaphragm in particular) and cranial nerve palsies. In contrast to the depolarization block of the cholinergic phase, the paralysis in the IMS is due to nondepolarization block. Difficulty in breathing occurs rapidly with the use of the accessory muscles of respiration (moving alae nasi, use of sternomastoids and other neck muscles in respiration) and if untreated, unconsciousness sets in followed rapidly by death due to respiratory failure. The IMS sets in approximately 1-4 days after poisoning, after the cholinergic phase. Complete recovery occurs within 4-21 days following adequate ventilatory care. Leon et al[8] performed a Medline search of published work on insecticide intoxication from 1965 to 1995 and found that the incidence of intermediate neurotoxic syndrome was 20-68% of affected patients, and that parathion was the causative agent in up to 75% of cases. In the series from China, 421

patients out of a total of 272 poisoned developed the IMS.

Delayed polyneuropathy (OPIDN)

The delayed polyneuropathy (OPIDN) usually sets in 14-28 days after exposure to an OP agent and is not associated with death but causes disability due to peripheral muscle weakness, recovery from which is not certain. The peripheral muscle weakness is symmetrical and there may be disturbances in sensation. The sensory component, if present, is milder than the motor component.[9]

The phosphorylation of an enzyme-neuropathy target esterase (NTE) in nerve tissue is considered to be responsible for the dysfunction.[10] NTE is a membrane-bound protein with high esterase catalytic activity whose physiologic function is not known. The catalytic activity of NTE is not essential to the health of nerve axons. However, modification of the structure of NTE initiates an irreversible polyneuropathy. This phosphorylated enzyme also undergoes 'aging'(see later).

OP insecticides may have a preference for inhibition of AChE (neurotoxic OP agents) or for phosphorylation of NTE (neuropathic OP agents). As inhibition of the two different enzymes is followed by distinct neurologic consequences in exposed subjects, it would be useful to distinguish between the neurotoxic and neuropathic OP agents. In experiments using neuroblastoma cell lines, it was found that neurotoxic OPs such as paraoxon and malaoxon were 100 times more potent in inhibiting AChE, compared with the ability to phosphorylate NTE. In contrast, concentrations inhibiting AChE and NTE were equipotent for neuropathy-causing OPs (e.g., mipafox). Mouse or human neuroblastoma cell lines may be considered useful in vitro models to distinguish esterase-inhibiting OP agents.[11]

Other effects of organophosphorus insecticides

1. Effects on the central nervous system. Following low-level exposure, complex changes may occur in higher intellectual functions such as memory, problem solving, and the interpretation of data. This may be accompanied by behavioral and psychologic changes. Eyer (1995)[12] considered that the most frequently reported neuropsychologic effects after OPintoxication are 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 the chronic psychiatric effects of varying intensity may persist for years. Duffy et al[13] studied the brain electrical activity of workers exposed to the OPcompound sarin after an interval of one 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 sleep. The authors suggested that the findings represented an unexpected persistence of known short-term OP actions and that taken in parallel with the reported long-term behavioral effects, OPexposure can produce long-term changes in brain function. Perfusion defects especially in the parietal lobe have been detected on single photon emission computed tomography (SPECT) following OP poisoning.[14] AChE, in addition to being an ACh-hydrolyzing enzyme, is also a neuromodulator participating in the phenomenon of neuronal plasticity, i.e., induction of long-term changes in synaptic efficacy. The loss of this nonenzymatic neuromodulatory role of AChE is considered to be the basis for the long-term alterations of cognitive function that may follow long-term occupational exposure to OP.[15]

Extrapyramidal manifestations (dystonia, rest tremor, cogwheel rigidity, choreo-athetosis)[16] may occur in some patients 4-40 days following OP poisoning. The symptoms disappeared spontaneously in about 1-4 weeks in those who survived. This was attributed to inhibition of AChE in the human extrapyramidal system that is rich in cholinergic neurons and AChE.

2. Altered immunity to infection. OP agents may have an effect on the human immune system. Casale et al[17] demonstrated that parathion suppressed both the primary IgM and IgG response to sheep erythrocytes in inbred and outbred mice. The suppression occurred after a dosage that produced cholinergic effects but was absent after a lower dosage.

The results demonstrated that OP-induced immunosuppression was associated with severe cholinergic stimulation probably from a direct action of ACh upon the immune system or it may be secondary to the toxic chemical stress associated with cholinergic poisoning. A marked impairment of neutrophil chemotaxis and a greater frequency of upper respiratory tract infection was demonstrated in workers occupationally exposed to OP in whom a decrease in both serum and RBC cholinesterase activity was observed.[18] Murray et al[19] reported influenza-like symptoms probably associated with OP toxicity in 23 patients after occupational exposure. Furthermore, many OP pesticides elicit auto-immune reactions and suppress the production of antibodies against vaccines.

3. Changes in metabolism and endocrine activity. Changes in glucose metabolism and in the diurnal pattern of plasma ACTH may occur.[20] Nonketotic hyperglycemia and glycosuria have been observed.[21] Significant decreases in serum concentrations of T3 and T4 and an increased TSH were observed in rats after malathion treatment.[22] Damage to seminiferous tubules and to the principal cells in the caput epididymis through its toxic effect on the Leydig cells and the clear cells of the cauda epididymis have been reported.[23] Several reports of pancreatitis following OP insecticide intoxication have appeared during the past two years.[24] It has been suggested that in OP poisoning, an elevation of serum amylase on the day of admission was predictive of subsequent respiratory failure.[25] Hypokalemia has been observed in some patients following intoxication.[20]

4. Effects on cardiac function. Cardiac complications such as hypotension, hypertension, arrhythmias (complete atrioventricular block, premature ventricular complexes, 'torsade de pointes'), and cardiac arrest often follow OP poisoning.[26] It has to be noted that hypoxia, metabolic acidosis, and electrolyte changes may compound these cardiovascular effects. It has been suggested that the accumulation of ACh at synaptic sites in the myocardium may produce negative inotropism due to interaction with the M2 muscarinic receptors.

Following OP insecticide intoxication, QTc prolongation indicated a poor prognosis (mortality rate of 19.6% compared with 4.8% in those without QTc prolongation) and a higher incidence of respiratory failure.[27] Experimental work in animals suggests a direct action of OP agents on the heart. The ECG changes following human intoxication did not show close correlation with the decrease in enzyme activity and cannot be influenced by atropine. The ECG alteration in animal experiments precedes the toxicologically relevant cholinesterase depression and is dose-dependent and cannot be induced by cholinergic or adrenergic drugs.[28]

5. Effects on reproduction. In experimental animals, OP poisoning during pregnancy causes prenatal and postnatal death and congenital abnormalities such as vertebral deformities, limb defects, polydactyly, intestinal herniae, cleft palate, and hydroureter.[29] In humans, following intoxication, during the third month of pregnancy abortion has been performed because continuation of pregnancy was considered hazardous.[30] Karalliedde et al[31] have described successful partus after severe OPintoxication that required ventilatory care during the second and third trimesters. However, there was no follow-up of the newborn nor of the mothers to determine as to whether there were unacceptable sequelae to the poisoning.

6. Miscellaneous effects. A variety of carboxyesterases are found in serum, liver, intestine, and other tissues. Although inhibition of one specific carboxyesterase, NTE, has toxic sequelae, no direct deleterious effects of inhibition of other carboxyesterases have been demonstrated. However, carboxyesterases may contribute markedly to the metabolic degra-

dation of OP insecticides such as malathion, and inhibition of these enzymes may potentiate the toxicity of some OP compounds.

A new variant of life-threatening OPtoxicity that produces a brief bilateral vocal cord paralysis was reported recently.[32] A two-year old boy developed progressive respiratory distress and stridor without generalized muscle weakness that progressed to complete airway obstruction for which endotracheal intubation was necessary. The vocal cord paralysis lasted two days. Isolated bilateral recurrent laryngeal nerve paralysis has been reported as a delayed complication of OP poisoning.[33]

The control of body temperature uses cholinergic pathways in the integration and central processing of thermal information, as well as in control of thermoeffector responses. After exposure to most OPs, rodents and other small species undergo a marked hypothermic response lasting up to 24 hours. Hypothermia has been noted in several case studies and was observed to have an incidence of 7%.[21] The precise etiology of the hypothermia has not been described and cannot be explained solely on the basis of inhibition of AChE.

Development of myopia in humans and pigmentary degeneration of the retina in experimental animals have been reported, but there has been no confirmatory reports. Changes in optical function may occur following prolonged exposure (e.g., two years) that would depress cholinesterase activity to 30% of normal.[34]

Exposure to OP pesticides was significantly associated with arthritis[35] after taking into account the effects of age, education, length of exposure, and poisoning history. Cerebellar disorder-ataxia developed about five weeks after acute exposure.[36] Initially no cholinergic features were observed.

The OP insecticide ethaphos interacted with mitochondrial oxidative metabolism[37] and inhibited the oxidation of succinate, alpha-glycerophosphate, pyruvate, and malate. The clinical consequences of such an effect are not known.

OP poisoning in children

Sofer et al[38] described 25 infants and young children intoxicated by carbamates and OPcompounds. The presenting signs and symptoms differed from those described in adults and were mainly related to severe CNS depression, coma, stupor, dyspnea, and flaccidity. Miosis, excessive salivation, tearing, sweaty cold skin, and gastrointestinal symptoms were less frequent, and bradycardia and fasciculations were quite uncommon on arrival in hospital.

Pathogenesis

Although the main symptomatology in the cholinergic phase is attributable to phosphorylation and the consequent loss of the catalytic function of AChE, which leads to accumulation of unhydrolyzed ACh, OP agents are known to inhibit other enzyme systems, the consequences of which are not known as yet. Restoration of AChE activity occurs by slow de novo synthesis of fresh enzyme and also to some extent as a result of spontaneous dephosphorylation of the inhibited enzyme. Spontaneous reactivation and thus recovery should occur faster following phosphorylation with dimethyl compounds when compared to diethyl compounds and thus recovery from poisoning would be more rapid. The rates for inactivation (phosphorylation) and reactivation (dephosphorylation) vary considerably for different OPagents and account for the differences in toxicity of the OP agents.[39] The loss of a radical makes the inactivated enzyme more stable so that spontaneous dephosphorylation does not occur. This process, referred to as 'aging,'has an important bearing on toxicity. With chemical warfare agents like soman, aging occurs very quickly. The spontaneous rate of reactivation can be accelerated by certain oximes that have a molecular structure which fits the surface of the inhibited AChE. Oximes can only be of benefit as long as some of the inhibited AChE remains in the 'unaged'form.

The IMS is now considered to be due to dysfunction at the neuromuscular junction (NMJ). Prolonged and severe cholinesterase inhibition that occurred during the IMS caused a decrement on repetitive nerve stimulation initially and then increment and finally normal responses. Necrotic fibers were noted in muscle biopsies but these were too sparse to explain severe muscle weakness.[40] In myasthenia gravis, repetitive nerve stimulation at low frequencies produce a decrement that increases up to the fourth or fifth response. In the Lambert-Eaton myasthenic syndrome, the amplitude of compound muscle action potential after a single stimulus is severely reduced, whereas it increases at high frequency repetitive stimulation.

The clinical and electrophysiologic features are best explained by combined pre- and postsynaptic dysfunction of neuromuscular transmission. Following the classic description of receptors at the NMJ by Bowman,[41] and the established association between Ca^{2+} release and muscle contraction, it was likely that the excessive Ca^{2+} mobilization that occurs in the presence of antiAChE agents probably caused a down-regulation or desensitization of the postsynaptic nicotinic receptor leading to the muscle weakness.[42] Nicotinic ACh receptor desensitization readily develops as a result of the accumulation of ACh at the NMJ.

In 1989, Kimura et al reported that contractile and noncontractile Ca^{2+} mobilization is generated simultaneously at the NMJ by nerve stimulation in the presence of anti-AChE agents.[43] Noncontractile Ca^{2+} mobilization occurs via the nicotinic ACh receptors only under such desensitizing conditions and depends upon the amount of ACh accumulated in the synaptic cleft. A subtype of the nicotinic ACh receptor, which is different from the usual muscle types of nicotinic ACh receptor, appears to operate the noncontractile Ca^{2+} mobilization at the NMJ.[43] The mechanism of noncontractile Ca^{2+} mobilization is completely different from that of contractile Ca^{2+} mobilization because the former requires the prolonged activation of nicotinic ACh receptors as a result of accumulating ACh in the synaptic cleft and is specifically blocked by competitive nicotinic antagonists, such as tubocurarine and pancuronium, at low concentrations (10-fold more potent) than that required to inhibit contractile Ca^{2+} mobilization. Furthermore, noncontractile Ca^{2+} mobilization is not due to Ca^{2+} release from the sarcoplasmic reticulum. The activation of protein kinase-A within muscle cells is essential to mobilize noncontractile Ca^{2+}. A skeletal muscle Na^{+} channel blocker selectively blocked contractile Ca^{2+} release without affecting noncontractile Ca^{2+} release.[43]

At present, the muscle weakness of IMS is likely to be due to the prolonged noncontractile Ca^{2+} influx and the consequent activation of protein kinase C, which enhances postsynaptic nicotinic receptor desensitization by depressing the contractile Ca^{2+} mobilization at the NMJ.

The delayed neurotoxic action of OP insecticides is independent of AChE inhibition, but related to the phosphorylation of a specific esteratic enzyme in the nervous tissue that has been termed "neurotoxic esterase" or "neuropathy target esterase" (NTE). The initial biochemical reaction is phosphorylation of NTE. The second essential step responsible for the neuropathy is the transformation of the phosphorylated enzyme to an aged form.[39] If compounds such as phosphinates and carbamates link to NTE before contact with a neuropathic OP, aging does not occur, preventing the development of the neuropathy.[39]

Biochemistry

AChE present in human erythrocytes (red blood cells, RBCs) is the same as that found in the target synapses, and changing concentrations of RBC AChE are assumed to mirror the effects of OP agents in the target organs provided the OP agent has equal access to blood and synapses. It cannot be assumed that the dysfunction at a cholinergic junction is linearly dependent upon the amount of AChE present as there are considerable reserves of the enzyme at all sites and the amount required for efficient functioning is very small in comparison to the total amount available. The range of depression of AChE or plasma cholinesterase (ChE) seen in patients with identical symptoms and signs may be very large.[44] Furthermore, the sensitivities of

AChE and ChE to OP agents differ and the use of whole blood may thus provide less accurate interpretations. However, in many field situations and in clinical practice, procedures using whole blood are more practical than those using separated RBCs. Usefulness of cholinesterase estimations are further limited due to the physiologic variations that occur within and between individuals in health and the influence of disease states, medications, and genetic variations on the enzyme. Thus, serial measurements would be of greater benefit. Further caution is required as there is no uniformly accepted standard technique; each method having its own "reference range."

In chronic exposure, depression of cholinesterase activity in blood to 80% is generally considered diagnostic of intoxication. When the depression is between 60% and 80%, there may be gastrointestinal symptoms, but there is considerable individual variation. Fasciculations and other neuromuscular signs and symptoms may develop with depression of AChE in excess of 80%.[44] Risk of death is high if the depression of cholinesterase is 90% or more. However, animals can survive 100% depression of the enzyme and men have had 90-95% depression of ChE and recovered without treatment.[44] In animals, bradycardia comes on at doses that will give 80-90% depression of AChE. Reduction to 70% or less of AChE indicates a health hazard. Acute mild exposure to OP may cause a reduction to 50% of normal activity of cholinesterase, moderate exposure causing a further reduction to 20% of activity. Very severe poisoning may reveal only 10% of activity.[5] Clinical recovery correlates well with RBC-AChE recovery to 30% of normal.[45] Plasma ChE recovers quickly, usually within 4 weeks; RBC-AChE takes longer and may not be restored to normal for several months. The recovery of AChE is approximately at the rate of 1% per day.

A study from Portugal concluded that serum cholinesterase (ChE) assays are useful in the diagnosis of OP poisoning and also in monitoring the clinical course.[46] ChE recovery above 10% of normal seemed to correlate with good prognosis.

Assay methods for cholinesterase activity vary[47] and include electrometric, colorimetric, and titrometric assays. The The World Health Organization (WHO) developed a field method for measurements in whole blood and plasma.[47] Fast methods exist for measurement in serum using paper strip.

In an evaluation of a spectrophotometric field kit (Test-Mate-OP), it was found that the field kit AChE (erythrocyte cholinesterase) estimation seems to be sufficiently repeatable for surveillance activities, whereas the field kit plasma cholinesterase (ChE) was not.[48] Repeatability of both tests seems to be too low for use in epidemiologic dose-response investigations.

Among the disadvantages of the presently used methods are that they cannot detect either low-level exposures with certainty or the structure of the agent and the extent of poisoning. In principle, OP-inhibited butyrylcholinesterase in human plasma is the most persistent and abundant source for biomonitoring of exposure to OP agents. Fluoride ions reactivate the inhibited enzyme readily at pH 4, converting the organophosphate moiety into the corresponding phosphofluoridate. Subsequent quantitation of the latter product provides a reliable, highly sensitive, and retrospective method for detection of exposure to OPs.[49]

Surveillance of occupational, accidental, and incidental exposure to OPpesticides using urine alkyl phosphate and phenolic metabolite measurements,[50] and the application of high-performance thin layer chromatography[51] have been recently discussed.

Measurement of OP agents

It is possible to measure levels of intact pesticides and their metabolites in the urine of workers exposed to OPcompounds, but such analysis is often unable to detect the parent compound due to the hydrolysis of the OP in the body.[52] Detection should be carried out as soon as possible after exposure, even though metabolites may persist for several days.[53]

Management

First aid measures should include removal of patient from the contaminated environment, removal of contaminated clothing, and washing of skin and eyes. Cardiorespiratory status should be assessed and resuscitation carried out if necessary. Pulse, blood pressure, ECG, SaO_2, respiration, and level of consciousness should be monitored. Oxygen therapy should be provided to maintain $PaO_2 > 10$ Kpa.

Prevent further absorption of insecticide

Activated charcoal is given to reduce absorption, even though the capacity of activated charcoal to adsorb OP compounds is not established. In acute fenthion poisoning, repeated activated charcoal administration until the absence of anticholinesterase capacity in the gastrointestinal fluid occurred was advocated by clinicians in Belgium.[54]

Arterial blood gases, red cell AChE and serum OP compound, serum electrolytes, creatinine and hematology tests should be measured, and a chest x-ray is recommended.

Atropine

Atropine acts as a physiologic antidote, effectively antagonizing the muscarinic receptor-mediated actions of excessive ACh such as increased tracheobronchial secretions, bradycardia, salivation, and bronchoconstriction. Atropine crosses the blood brain barrier and counteracts the effects of ACh accumulation in the central nervous system. The initial dose should be 2 mg intravenously and repeated at 5-10- minute intervals until signs of atropinization occur—a pulse rate over 80 beats/min, and dilatation of pupils from the initial constricted pupils. Atropine therapy should be maintained until there is complete recovery.

Atropine was shown to enhance neuromuscular transmission and/or transmitter release, possibly by acting on muscarinic presynaptic inhibitory receptors, which are involved in the feedback mechanism of transmitter release.[55] This observation is of relevance in OP poisoning as the pathologic basis is the accumulation of ACh at the NMJ. It has been shown that a lower than traditional dose of atropine used over a shorter duration at a hospital in China was associated with a lower complication and fatality rate.

Oximes

Oximes such as pralidoxime are useful in the treatment of OP poisoning[56] and three actions have been attributed to pralidoxime[29] (a) reactivation of cholinesterase by cleavage of phosphorylated active sites, (b) direct reaction and detoxification of unbounded organophosphate molecules, and (c) endogenous anticholinergic effect in normal doses.

It is believed that when effective concentrations of oxime are achieved, the balance between aging and reactivation reaction rates for the inhibited AChE is altered in favor of the latter. Thus benefit will ensue even if oxime therapy is commenced or continued several days after intoxication. Therapeutic concentrations of the oxime should be maintained to regenerate as much active enzyme activity as possible until the OP compound has been eliminated.

The reactivation action of pralidoxime is most marked at the NMJ. It does not reverse the muscarinic manifestations of OP poisoning and has a short half-life (1.2 hours) when administered intravenously. Oximes being ionized compounds do not cross the blood brain barrier easily and reactivation of brain AChE is less than 10%.[57] However, that the limited passage of the oxime to the brain may have a significant, albeit small effect and prompt improvement has been reported following intravenous infusion of pralidoxime chloride.[58]

Pralidoxime in large doses can produce neuromuscular block and even inhibition of AChE.[5] There exists some controversy regarding the use of pralidoxime in OP poisoning[59,60] and the specific temporal sequence for administration of atropine and pralidoxime.

The therapeutic effect of oximes seemed to depend on the

plasma concentration of the OP agent with the benefits being minimal at high concentrations of OP in the blood.[61] High frequency of cardiac arrhythmias was observed in patients who received high cumulative doses of atropine and obidoxime. Impairment of liver function was significantly higher in patients who received high cumulative doses of obidoxime.[62]

Diazepam

Some reports have indicated that benzodiazepines are potentially useful as antidotes to poisoning by ChE inhibitors.[63] Diazepam has been useful in the management of convulsions after OP poisoning and in the support of ventilatory care.[5]

Other drugs shown to be useful in experimental OP poisoning are clonidine and fluoride. However, no clinical trials have been done. The use of resealed erythrocytes containing phosphoridiamidate has been found to be successful in treating OP poisoning in experimental animals. The protection resulted in increased survival rates and a reduction in centrally mediated symptoms.

Environmental pollution

Pollution of the environment and the effect of OP compounds on vegetation, water supplies, aquatic life, and in particular, on agricultural products have been a growing concern in industrialized countries. Biochemical interest has been directed towards the detection of OPcompounds in the environment and in food products.[64]

Mitochondrial transmembrane electric potential (delta psi) of isolated mitochondria was used to evaluate the toxicity of some chemicals, including OP agents.[65] In a study of approximately 200 citrus samples , 12 OP pesticide residues were detected in 32% of the samples and 6.9% exceeded the European Union maximum residue levels (MRLs).[66]

Oysters and mussels as filter feeders are used as bioindicators of contamination in the monitoring of pollutant effects. The oyster has two cholinesterases. 'A' cholinesterase (apparent molecular weight 200 kDa) is anchored to the membrane via a glycolipid, is not glycosylated but is sensitive to OPand carbamate inhibitors. 'B'cholinesterase (molecular weight 330 kDa) is hydrophilic, glycosylated, and highly resistant to OPand carbamate inhibitors.[67] It is of interest that some animals do possess a cholinesterase resistant to OP compounds.

Conclusion

OP insecticides are a major health hazard globally. In developing countries, which use 20% of the global pesticide production, 90% of the morbidity and mortality associated with pesticides is encountered. Atropine and Pralidoxime have continued to be the major therapeutic tools for over 25 years. Today, the disadvantages of atropine and pralidoxime are known and many clinicians have questioned the benefits of such therapy. Despite improvements in intensive care and related disciplines, the mortality associated with OP insecticide poisoning has not decreased. Research has been limited due to paucity of biochemical analytic methods and of the technology in general in the developing countries where OPpoisoning is most frequent. Although 'bench' research continues in the developed countries, the transfer of information has been ineffective. Possibly, the way forward is for collaborative research and study between institutions and organizations in the developed and developing countries.

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