Organophosphorus Poisoning in Agricultural India – Status in 2005

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India is a predominantly agrarian country with about 60-80% rural population. Pesticides are routinely used for advanced farming. These are readily available over the counter. Therefore, a pesticide is an easy access source for suicidal purpose particularly after trivial family squabbles. Such little petty quarrels often that result in consumption of pesticide for suicide purpose is a matter of routine news in local dailies. Poisoning is seldom included as a priority for health research in India, though every year, hundreds of people are loosing their lives prematurely from pesticide poisoning.1 Vomiting soon after consumption of pesticide and with its smell easily detected even by a lay person poses no diagnostic difficulty. Thereby, quite often, the victim is brought to a health centre within an hour of consumption of the pesticide – usually Organo-Phosphorus Compounds (OHPs) and carbamates. This is the “Golden Hour” for clinical intervention, before irreversible “ageing” of toxic compounds in blood occurs. Primary Health Centers in India are known for lack of drugs, doctors and application of evidence-based treatment. More than 100 such heterogenous compounds exist. These can also be used as weapons for chemical warfare.

Organophosphorus compounds and carbamates are a family of compounds that share structural similarities. The kinetics of each group are highly dependent on multiple physical factors including route of administration (ingestion, injection, inhalation, transdermal and transmucosal absorption), distance from target organs, local versus systemic metabolism & activation, route of elimination, endogenous hydrolysis, and consumption of the compound by various nonspecific esterases before reaching target organs. Structural considerations include the groups attached to the sulfur, carbon, or phosphorus moiety, the tightness of the bond to the central atom, and the affinity of the compound for cholinesterases.2 Majority of agents show some signs and symptoms of toxicity within 6 to 12 hours after exposure with the exception of the highly fat-soluble compounds (fenthion, difenthion, chlorfenthion). The fat-soluble compounds may not manifest toxicity for several days to weeks because the toxic substance must be “leached out” of the fat until a sufficient amount of cholinesterase is inhibited to cause symptoms. Other agents that may have delayed onset of symptoms include those compounds that require hepatic activation to convert the substance to its active toxic state (e.g., parathion to paraoxon).2

Patients will remain clinically ill as long as there is active toxin available to bind to any free cholinesterase and depress the cholinesterase to less than 20 per cent activity. This is affected by the rate of endogenous hydrolysis (ranging from months for organophosphates to hours with carbamates), amount of unbound nonspecific esterases available to scavenge free toxin, and circulating pralidoxime. With the exception of the fat-soluble agents, it was initially believed that most organophosphorus residues were eliminated within the first 48 hours after exposure. Newer data suggest these residues may remain for days to weeks, even after successful treatment of initial symptoms. AChE, if not regenerated by nucleophilic oximes such as the antidote pralidoxime, must be generated at the nerve terminal, a process that may take several months. Butylycholinesterase (BuChEs) are hepatically synthesized acute-phase proteins that can be replaced within several weeks. Toxicity, however, is dependent on AChE activity.2

Organophosphorous compounds and carbamates inhibit the function of carboxylic ester hydrolases such as chymotrypsin, AChE, plasma or BuChE (pseudocholinesterase), plasma and hepatic carboxylesterases (aliesterases), paraoxonases (asterases), and other nonspecific esterases within the body. Both organophosphates and carbamates can bind into the acyl pocket at the active site of AChE. The binding of a phosphate (organophosphate) or carbamyl (carbamate) group to the serine amino acid at the active site of ACh changes the configuration of the enzyme molecule, stabilizing it and preventing it from functioning. The carbamyl group from a carbamate will spontaneously dissociate within 24 hours, leaving a functional enzyme. However, spontaneous regeneration of phosphorylated AChE requires days to months; so, from a physiologic perspective, an enzyme phosphorylated by an organophosphate is permanently inactivated. Function can only be restored if a new enzyme is created or an antidote displaces the phosphate moiety. Because enzyme regeneration takes weeks, the only real physiologic option is to use an antidote.2 Over

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time, organophosphorous compounds can permanently alter the shape of the acyl pocket so that endogenous hydrolysis of the serine-phosphate bond cannot occur and antidote function becomes limited. This is called “aging.” During the “aging” reaction, the acyl group is lost from the phosphorylated enzyme and the pocket shape change becomes permanent. Carbamates dissociate from the AChE molecule within 24 hours, so they do not cause aging. They also will not pass readily through the blood-brain barrier and thus have limited CNS toxicity.²

The treatment of patients who consumed lethal doses of various organophosphorus compounds still remains a great challenge to clinical toxicologists. The oximes in combination with atropine and diazepam are an integral part of the treatment of acute intoxications with organophosphate. Treatment with atropine, which relieves the muscarinic effects of acetylcholine and anticonvulsive agents (diazepam) is well established. However, the effectiveness of oxime compounds in counteracting the effect of intoxication in still a matter of debate. Currently treatment of cholinesterase inhibitor poisoning is directed toward supportive care, decontamination, restoration of oxygenation, treatment of muscarinic signs and symptoms, and antidotal therapy to regenerate AChE. Because organophosphates will penetrate normal latex or polyvinyl gloves, nitrile or neoprene (chemical resistant) gloves are recommended. However, often copious, ongoing vomiting prevents further gastrointestinal measures, including use of activated charcoal. Clothing is toxic waste and needs to be double bagged. The patient should be washed down with copious amounts of water. Gentle cleaning with soap and water is effective and will not abrade the skin and enhance absorption. Atropine, a competitive ACh antagonist at the postsynaptic muscarinic nerve membrane, will dry respiratory secretions and bronchodilate.²

Pralidoxime, the only antidote that is available in India, is one of a class of nucleophilic oximes that regenerate AChE by removing the phosphate moiety from the acyl pocket. Pralidoxime will also act as a scavenger for additional nonbound organophosphate. Although pralidoxime is less effective in the case of “aged” AChE, the time to complete inactivation of the AChE by aging is not fully known and may vary between different agents. Consequently, there is no restriction to using pralidoxime even if more than 24 to 48 hours have passed. Both maintained serum levels greater than 4 mg/L.³ Data in this regard is scant and prior to the current trial in this issue of JAPI few randomised clinical trials have been published.³ However even recent Cochrane concluded that current evidence is insufficient to indicate whether oximes are harmful or beneficial in the management of acute organophosphorus pesticide poisoning.⁴ A much larger RCT is required to compare the World Health Organization recommended pralidoxime regimen (>30 mg/kg bolus followed by >8 mg/kg/hr infusion) with placebo. There are many theoretical and practical reasons why oximes may not be useful to patients with overwhelming self-poisoning.⁵ Such a study will need to be designed with pre-defined sub-group analysis to allow identification of patient sub-groups that may benefit from oximes.⁶ The CNS effect of organophosphate intoxication may be partially treated by pralidoxime. Although pralidoxime is a polar compound, there is evidence to suggest that it has a positive effect on the CNS.²

In the current issue, a trial done by Vellore group is probably the third trial in the literature in which placebo versus pralidoxime in the management of organophosphorus poisoning.³ The major limitations of the Vellore trial is small sample size of 10 (5 placebo, 5 on PAM) and 11 patients only in moderate and severe group respectively and due to cost constraints smaller subtherapeutic (4 gm/day instead of the 8 gm WHO norm) dose of PAM was used in moderate group. Choline esterase from whole blood was not done but acute phase reactant BChE levels were measured and in eleven out of twenty one cases the poison was not even known. Irrespective of modern investigations and intensive treatment including pralidoxime the fatality rate is still 7-12%. Pralidoxime has been utilized in an empirical way needs better validation with more randomised clinical trials (RCT) in mild to moderate case of organophosphorus poisoning. This trial confirms in tertiary care centers that pralidoxine did not add any benefit moderate to severe organophosphorous poisoning. However early administration of pralidoxine within first hour of consumption of drug may be of some beneficial if it is administered at primary health center where victim is brought within one hour of consumption of drug. Because once the phosphorylated enzyme has “aged” then the phosphate group becomes irreversibly bound to the enzyme and oxime therapy is no longer as effective. Based on animal data, a serum level 4 microgram per liter is required for minimum therapeutic threshold. Which can be easily obtained by infusion of 500 mg per hour what is done in present reported trial.³ Singh S et al in their case series reported that continuous 2-PAM infusion along with aggressive atropinisation after initial decontamination improved the outcome but not the duration of mechanical ventilation in severely intoxicated patients.³ Pralidoxime is expensive and not free from toxicities. The negative results of PAM therapy should be excluded or confirmed by arranging a multicentres mega trial or by meta-analysis.⁵

There are attempts to produce newer antidotes with oximes like obidoxime, HI 6, HLo 7, etc. Intramuscular autoinjector oxime will be the modern answer to the modern rural health provider where even a nurse can inject the antidote. In animal model a organophosphate hydrolases, break down organophosphate and speed up the reactivation of acetyl cholinesterase; reversible anticholinesterase (carbamate pyridostigmine) able to reduce re-inhibition of acetyl cholinesterase and glutamate antagonist and agonist for adenosine and alpha-2 adrenergic receptors to limit damage to the central
nervous system. It is surprising to note that no new antidote have been tested in clinical trials in the last 30 years. The UK’s Welcome Trust is funding two large randomized controlled trial of activated charcoal and pralidoxime in Sri Lanka, though the results are not yet out. Whatever the antidotes available it is most important that all primary health centers should be well equipped for, to treat this emergency including, simple tracheal intubations and manual ventilation by Ambu bag. Rural health care professionals including physicians ought to be imparted adequate training regarding early diagnostic signs of poisoning, including central nervous system manifestations. Prevention is mother of cure. There is a strong case for framing rules that will necessitate maintenance of for issuance register by a vendor for quantity of pesticide delivered and the name of the client. The pesticide labelling with skull connoting a poisonous substance may also need to be reworked. It is time for Government to phase out WHO class I and WHO class II pesticides from the market and replace them with safer pesticides. There is a need to shift our health care focus to agricultural India and develop an integrated pesticide management system. We can save lives by safer pesticides and use user-friendly antidotes.

REFERENCES


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