SUMMARY

Organophosphate insecticides (OPI) constitute one of the most widely used classes of pesticides being employed for both agricultural and landscape pest control.

Presently, more than 100 different OPI are used worldwide. The advantage of a lower environmental stability, compared to organochlorine compounds (e.g. DDT), and a high effectiveness against different insect species is accompanied by the disadvantage of high mammalian toxicity.

Organophosphate insecticides remain a major health concern due to the large number of annual acute poisoning. Indeed, according to the data of the world Health organization, there are more than 3 millions of organophosphate intoxications annually and more than 220.000 deaths.

Acute organophosphorus poisoning occurs after dermal, respiratory, or oral exposure to either low volatility pesticides (e.g. chlorpyrifos, dimethoate) or high volatility nerve gases (e.g. sarin, tabun).

Occupational and accidental OP exposure are the main causes for mild poisonings, whereas severe cases are mostly due to suicidal attempt and self-poisoning.

Chronic toxicity of organophosphate usually occurs in agriculture workers who have regular contact with these compounds, but may also occur in individuals who have repeated contact with excessive amounts of insecticides in their living environments.

Inhibition of acetylcholinesterase at synapses results in accumulation of acetylcholine and overactivation of acetylcholine receptors at the neuromuscular junction and in the autonomic and central nervous systems.

Early clinical features (the acute cholinergic crisis) reflect involvement of the parasympathetic system and include bronchorrhoea, bronchospasm, miosis, salivation, diarrhea, urination, and hypotension. Features indicating involvement of the neuromuscular junction (muscle weakness and fasciculations) and central nervous system (seizures, coma, and respiratory failure) are common at this stage. Respiratory failure may also occur many hours later, either separated in time from the cholinergic crisis (intermediate syndrome) or merged into the acute cholinergic crisis.

The acute poisoning mechanisms are realizable via AChE inhibition. The intermediate syndrome is considered to be a delayed complication of severe acute poisoning, and organophosphorus induced delayed polyneuropathy (OPIDP) may be the consequence of both acute and chronic poisoning with some OP–neuropathic agents, the typical biochemical sign of their action being inhibition of the so called neurotoxic esterase (NTE).

Patients with intermediate syndrome are at risk of developing of respiratory failure and may need respiratory support. The prognosis of delayed polyneuropathy is usually good as it affects distal muscles without affection of respiration.

Children are more susceptible to organophosphate poisoning than adults and show more frequent central nervous manifestations than

classical muscarinic effects due to susceptible central nervous systems and low levels of cholinesterase and paraoxonase enzyme.

Cardiac complications were observed in ECG abnormalities such as QT interval prolongation, ST-T change, and pleomorphic ventricular tachyarrhythmia of the torsade de pointes.

Organophosphorus poisoning is associated with a high mortality rate due to respiratory failure, dysrhythmias, and multi-organ failure.

Also OP pesticides could affect many other organs such as immune system, urinary system, reproductive system, pancreas, liver as well as hematological and biochemical changes.

Patients exposed to sufficient levels of OP compounds that are toxic to the respiratory system will indicate vague symptoms of chest tightness or pressure and show combinations of wheezing (expiratory, inspiratory, or both), rales, and rhonchi.

These compounds exhibit respiratory and pulmonary toxicity through direct inhalation and indirect effect on all aspects of respiration through systemic toxicity.

Acute pancreatitis secondary to OPI intoxication is a rare and generally well-course condition. Other associated abnormalities with elevated amylase level such as polymorphnuclear leucocytosis, hyperglycaemia and elevated transaminases were reported.

Organophosphorus insecticides generally cause an increase in activities of ALP, ALT and AST enzymes and also cause an increase in total cholesterol and total lipid levels.

It has been postulated that OPI produced oxidative stress in different tissues, such as kidney of rats and mice, through the formation of reactive oxygen species (ROS). OPCs cause increase of malondialdhyde the end product of lipid peroxidation which suggests lipid peroxidation induced nephrotoxicity.

Acute OP poisoning in rats induced a hypothyroid state consistent with euthyroid sick syndrome. Also disrupt thyroidal activity resulted in decreased serum T_3 and T_4 and increased thyroid- stimulating hormone levels.

Organophosphate insecticides induced parotitis can occur, hyperamylasemia and hyperlipasemia were found. Also there are several established immune system effects of the various OPI.

Pesticides cause various histopathological and cytopathological changes in the male reproduction system. Also organophosphates have been show to damage the ovaries of various species, decrease ovarian weights, as well as reduce the numbers of various follicle types in the mouse ovary.

Acute OP poisoning is the most common reason for admission into the emergency department and medical intensive care unit. So identification of severity at an early stage followed by prompt treatment can prevent the late respiratory and cardiac failures associated with OP poisoning.

A number of systems have been proposed for predicting outcome in OP poisoning. Many are reliant on laboratory tests and are, therefore, less useful in resource poor locations. Others that use clinical parameters have only been validated using small numbers of patients.

Acute Physiology and Chronic Health Evaluation (APACHE) II, simplified acute physiology score (SAPS) II and Glasgow Coma Scale (GCS) scoring systems have been reported to predict the mortality in OP poisoning with great success.

Currently, the only practical diagnostic study for verifying cholinesterase inhibitor poisoning is a measurement of cholinesterase activity in readily accessible tissue, such as the plasma and erythrocytes. In some cases, measurement of lymphocyte NTE has been predictive of subsequent onset of delayed neuropathy. However, available data are insufficient to suggest the use of NTE measurement in blood for biological, monitoring of individuals exposed to neuropathic OPCs. Some authors propose β-glucoronidase (BG) as a much more susceptible and rapid exposure biomarker than serum cholinesterase. Blood AChE is more sensitive at low OP exposures, whereas BG is very sensitive at high exposure of severe poisoning.

Urinary metabolites have been used as monitors of exposure to nerve gases and would be effective in insecticide exposure regulation with some considerations. Leukocytosis is reported during intoxication and the leukocytic count returns to normal level after treatment. Serum enzyme profile disturbance was also reported.

Treatment of organophosphate consists mainly of intensive respiratory and general supportive measurements, decontamination (e.g. gastric lavage), specific antidotes as atropine and cholinesterase reactivators (oximes) and treatment of complications. It should be initiated immediately on clinical suspicion without waiting for blood investigations.

Atropine is still the antimuscarinic antidote of choice, which antagonizes muscarinic and central manifestations. It is administered with initial dose of 1-2 mg IV in adults (0.01 mg/kg in children) and repeated every 5 minutes until muscarinic manifestations subside as regard control of respiratory secretions not pupillary size measurement. Atropine therapy should be continued for at least 24 hours and should be tapered before being discontinued to avoid relapse of manifestations. Other alternate routes as inhalation of nebulized atropine in adults and interaosseous route in children may be used when IV route is inaccessible.

Oximes are potent cholinesterase activators including: pralidoxime (2- PAM), obidoxime, trimedoxime and H series (HI-6, HLO-7). Oximes can lower the acetylcholine concentrations and reverse both muscarinic and nicotinic effects. The indication of 2-PAM is muscle weakness and respiratory paralysis. The initial loading dose of 2-PAM in adults is 1-2 gm in 100 ml of 0.09% sodium chloride solution by IV route over 10-30 min. (20-40 mg/kg over 30 min. in children) to be followed by a continuous 2–PAM infusion (500 mg/h in adults and 10-20 mg/kg/h up to 500 mg/h in children) in serious cholinergic poisoning. In most cases, pralidoxime is continued for a minimum of 24 hours after symptoms have resolved. The effectiveness of oximes is a matter of controversy and is limited by the type and dose of OP, the time to start therapy and the dose of oximes.

The ‘ageing’ of inhibited AChE is particularly important, since aged enzyme cannot be reactivated by oximes. The therapeutic window for oximes is, therefore, very much determined by the rate of ageing.

Diazepam prevents and treats organophosphorus-induced seizures. Sodium bicarbonate is a promising antidote from animal and

human studies (adjunctive to other antidotes) and may be beneficial by many proven mechanisms, but no strong clinical evidence is available. Magnesium sulphate, clonidine, NMDA receptor antagonist, organophosphorus hydrolases and fresh frozen plasma still struggling with conducting an evidence-based trials.