Toxicokinetics of Organophosphours Compounds

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ABSTRACT

Organophosphorus (OP) compounds constitute a heterogeneous category of chemicals specifically designed for the control of pests, weeds or plant diseases. Organophosphorus (OP) compounds are widely used in agriculture, medicine and industry. OP pesticides, in addition to their intended effects like the control of insects or other pests, are sometimes found to affect non-target organisms including humans. Exposure to OPs is also cause of long-term damage to the nervous system, reproductive and respiratory systems with reports of poor mental health and deficits in memory and concentration. Because of the serious environmental problems resulting from the use of pesticides in the agricultural sector, several countries are seeking employ biological and other nonpolluting methods for combating pests.

INTRODUCTION

Organophosphorus (OP) compounds are used as pesticides, herbicides, fungicides, rodenticides and disinfectants and chemical warfare agents in the form of nerve gases. [4]. Pesticides any substance used to prevent destroy and repel the pest such as insects, rodents, nematodes etc. is called as pesticide. [70, 69]. A pesticide may be a liquid (mist or spray), solid (dust, granule or bait) or gas (vapour) applied to control unwanted insects, ticks, mites, plants or animals in a given area [70]. Acute poisoning by these agents is a major global clinical problem, with thousands of deaths occurring every year [11].

Most of the OP pesticide poisoning and subsequent deaths occur in developing countries following a deliberate self-ingestion particularly in young, productive age group ,as highly toxic pesticides are readily available at the moments of stress [30].

Global status:

The organophosphate compounds are most commonly associated with serious human toxicity, for more than 80% of pesticide-related hospitalizations [21]. In contrast to the past, when chlorinated hydrocarbon compounds such as DDT were commonly used, organophosphate insecticides have become increasingly popular for both agricultural and home use because their unstable chemical structure leads to rapid hydrolysis and little long-term accumulation in the environment. This widespread use, however, has resulted in increased numbers of human poisonings. Through the 1970s, the Environmental Protection Agency estimated that 3,000 hospitalizations per year were required for insecticide poisoning in the United States, with a fatality rate of 50% in the paediatric age group and 10% in adults [23,31]. In1983 data from the American Association of Poison Control Centres indicated that the national incidence of insecticide exposures was 77,000, of which 33,000 involved organophosphates [34]. The continued use of such chemicals will likely increase these statistics in the future.

The first global estimates of the extent of pesticide poisoning were published in 1990 by the World Health Organisation [35]. Based on extrapolations from limited data, it was estimated that 3 million cases of pesticide
poisonings occurred world-wide annually with 220,000 deaths, the majority intentional. The WHO estimates, based on 2001 data, that 849,000 people die globally from self-harm each year [36]. However, poisoning is the commonest form of fatal self-harm in rural Asia, accounting for over 60% of all deaths [44,41,37] and is of far greater importance than hanging, and other physical forms of self-harm. Furthermore, a review of poisoning studies reveals that pesticides are the commonest means of self-poisoning in many rural areas and associated with a high mortality rate [45]. A national survey in Bangladesh showed that 14% of all deaths (3971 of 28,998) of women between 10 and 50 years of age were due to self-poisoning, the majority with pesticides [46]. The problem is particularly severe in Sri Lanka [47] where pesticide poisoning was the commonest cause of hospital death in six rural districts during 1995 [53]. In many countries, the widespread availability of acutely toxic pesticides used in agriculture has made selection of pesticides as the agents of choice for self-harm well known to both health care workers and public health authorities [59,57,58].

Classification of pesticides:
1. Organophosphorus compounds were first developed by Schrader shortly before and during the Second World War. They were first used as an agricultural insecticide and later as potential chemical warfare agents [67]. These compounds are normally esters, thiol esters, or acid anhydride derivatives of phosphorus containing acids.
2. Of the more than 100 OP pesticides used worldwide, the majority are either dimethyl phosphoryl or diethyl phosphoryl compounds (WHOTask Group on organophosphorus Insecticides. Organophosphorus insecticides:

Nerve gas compounds like tabun, sarin, and soman are highly potent synthetic toxic agents of this group. Commonly available dimethyl and diethyl OP compounds are listed in Table 1.

Table 1: Main types of OPCs.

<table>
<thead>
<tr>
<th>Dimethyl Ops</th>
<th>Diethyl OPs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parathion</td>
<td>Methyl parathion</td>
</tr>
<tr>
<td>Diazinon</td>
<td>Dichlorovos</td>
</tr>
<tr>
<td>Chlorpyrifos</td>
<td>Dimethoate</td>
</tr>
<tr>
<td>Dichlorfenthion</td>
<td>Malathion</td>
</tr>
<tr>
<td>Coumaphos</td>
<td>Fenthion</td>
</tr>
</tbody>
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Classification of pesticides is done on the following ways, i) According to nature of hydrocarbon chains

Aliphatic Pesticides: Hydrocarbon chain containing pesticide is aliphatic in nature. They may have single bond between two carbon atoms or may also have double bond between two carbon atoms. e.g. Monocrotophos.
Aromatic Pesticides: Aromatic ring is present in hydrocarbon chain. E.g. Parathion

ii) According to pests against they are used According to this type pesticides are classified in following ways.

Insecticides: These are pesticides used against insects. E.g. Dimethoate
Rodenticides: These are the pesticides used against rodents such as mice, rat, squirrels etc. e.g. Warfarin.
Miticides: These are also called as acaricides. These are pesticides which are used against mites. Mites are minute, transparent parasites. e.g. Ethion.

Fungicides: These are pesticides used against fungi. e.g. Dithiocarbamates.
Herbicides: These are also called as weedicides, weeds are the unwanted plants. e.g. Alachlor

iii) According to mode of action: According to mode of action pesticides have following types [35]

Stomach or internal pesticides: These are pesticides which kill the pest on its ingestion. E.g. DDT
Contact or external pesticides: These are pesticides which kill the pests on its contact externally. e.g. Malathion

Fumigants: These are the pesticides which emit poisonous vapours and paralyze respiratory system of the pest. E.g. Benzene-hexachloride (BHC)

dessicants: These are pesticides which kill pest by their dehydration. E.g. Calcium phosphate.
Chemosterilants: These are chemicals which affect reproductive system of pest and make them sterile. e.g. Thiotepa.

Repellents: These are chemicals which repel the pest and protect the plant. E.g. Thiram.

iv) According to functional group present in pesticide: According to this there are following types of pesticides [35]

Organ chlorine pesticides: These pesticides contain C–Cl bond. E.g. DDT (Dichlorodiphenyl-trichloroethane).
Organosulphur Pesticides: These pesticides contain C=S or –C–O–S bond. e.g. Endosulfan.
Carbamates: These pesticides contain –O–C=O bonding. e.g. Carbaryl (Sevin).
Organophosphorus Pesticides: These pesticides contain CO PO3 bonding. [59] 35/III e.g. Dimethoate.
Routes of toxicity:

OP pesticide exposure occurs through inhalation, ingestion and dermal contact [27]. Because OP pesticides disintegrate quickly in air and light, they have been considered relatively safe to consumers [27]. However, OP residues linger on fruits and vegetables [27]. Certain OP pesticides have been banned for use on some crops, for example methyl parathion is banned from use on some crops while permitted on others [27]. The Environmental Working Group has developed lists for concerned consumers, identifying crops with the highest pesticide residue quantities and the lowest. The "Dirty Dozen" crops are updated yearly and in 2012 included apples, celery, sweet bell peppers, peaches, strawberries, imported nectarines, grapes, spinach, lettuce, cucumbers, domestic blueberries and potatoes (EWG’s 2012). Forty-five fruits and vegetables are listed by the Environmental Working Group as being regularly found with pesticide residue associated with OPs.

Mechanism of toxicity:

The toxic mechanism of OP compounds is based on the irreversible inhibition of acetyl cholinesterase due to phosphorylation of the active site of the enzyme. This leads to accumulation of acetylcholine and subsequent over-activation of cholinergic receptors at the neuromuscular junctions and in the autonomic and central nervous systems. The rate and degree of AChE inhibition differs according to the structure of the OP compounds and the nature of their metabolite. In general, pure thion compounds are not significant inhibitors in their original form and need metabolic activation (oxidation) in vivo to oxon form. For example, parathion has to be metabolized to paraxon in the body so as to actively inhibit AChE [26].

The toxic mechanism of OP pesticides differs from that of carbamates which inhibit the same enzyme reversibly and are sometimes useful as medicines (neostigmine, pyridostigmine) as well as insecticides (carbaryl) [68].

After the initial inhibition and formation of AChE-OP complex two further reactions are possible: (1) Spontaneous reactivation of the enzyme may occur at a slow pace, much slower than the enzyme inhibition and requiring hours to days to occur. The rate of this regenerative process solely depends on the type of OP compound: spontaneous reactivation half-life of 0.7 hours for dimethyl and 31 hours for diethyl compounds.

In general, AChE-dimethyl OP complex spontaneously reactivate in less than one day whereas AChE-diethyl OP complex may take several days and reinition of the newly activated enzyme can occur significantly in such situation. The spontaneous reactivation can be hastened by adding nucleophile reagents like oximes, liberating more active enzymes. These agents thereby act as an antidote in OP poisoning [12]. (2) With time, the enzyme-OP complex loses one alkyl group making it no longer responsive to reactivating agents. This progressive time dependent process known as ageing. The rate of ageing depends on various factors like pH, temperature, and type of OP compound; dimethyl OPs have ageing half-life of 3.7 hours whereas it is 33 hours for diethyl OPs. The slower the spontaneous reactivation, the greater the quantity of inactive AChE available for ageing. Oximes, by catalyzing the regeneration of active AChE from enzyme-OP complex, reduce the quantity of inactive AChE available for ageing. Since ageing occurs more rapidly with dimethyl OPs, oximes are hypothetically useful before 12 hours in such poisoning [12]. However, in diethyl OP intoxication they may be useful for many days.

Delayed Polyneuropathy: Delayed polyneuropathy is an uncommon consequence of severe intoxication or intermittent and chronic contact with OP pesticides as in occupational exposure [38]. It is due to inhibition of neuropathy target esterase (NTE) enzyme in nervous tissues by certain OP compounds.

Many locally available OPs have negligible NTE inhibitory effect except chlorpyrifos which causes intermediate degree of inhibition. Delayed polyneuropathy is often unrecognized in humans and many times the clinical features are easily overlooked. Clinical manifestations are of distal symmetric sensory-motor polyneuropathy (distal weakness, parasthesia, ataxia, diminished or absent reflexes). The symptoms usually begin 2-5 weeks after exposure to the chemical, and may last for years [26].

Apart from these well-defined neural syndromes, OP pesticides can also cause chronic neurotoxicity and behavioural impairment in some patients.

Signs and symptoms:

The health effects associated with organophosphate poisoning are a result of excess acetylcholine (ACh) present at different nerves and receptors in the body because acetylcholinesterase is blocked. Accumulation of ACh at motor nerves causes overstimulation of nicotinic expression at the neuromuscular junction. When this occurs symptoms such as muscle weakness, fatigue, muscle cramps, fasciculation, and paralysis can be seen. When there is an accumulation of ACh at autonomic ganglia this causes overstimulation of nicotinic expression in the sympathetic system. Symptoms associated with this are hypertension, and hypoglycemia. Overstimulation of nicotinic acetylcholine receptors in the central nervous system, due to accumulation of ACh, results in anxiety, headache, convulsions, ataxia, depression of respiration and circulation, tremor, general weakness, and potentially coma. When there is expression of muscarinic overstimulation due to excess acetylcholine at muscarinic acetylcholine receptors symptoms of visual disturbances, tightness in chest, wheezing due to
bronchoconstriction, increased bronchial secretions, increased salivation, lacrimation, sweating, peristalsis, and urination can occur [16,36].

The effects of organophosphate poisoning on muscarinic receptors are recalled using the mnemonic SLUDGEM (Salivation, Lacrimation, Urination, Defecation, Gastrointestinal motility, Emesis, Miosis). An additional mnemonic is MUDDLES: miosis, urination, diarrhea, diaphoresis, lacrimation, excitation, and salivation [40].

The onset and severity of symptoms, whether acute or chronic, depends upon the specific chemical, the route of exposure, the dose, and the individuals ability to degrade the compound, which the PON1 enzyme level will affect.

Other Toxic Effects Of OPCS:

a. Reproductive effects:

Certain reproductive effects in fertility, growth, and development for males and females have been linked specifically to OP pesticide exposure. For those males exposed to OP pesticides, poor semen and sperm quality have been seen, including reduced seminal volume and percentage motility, as well as a decrease in sperm count per ejaculate. In females menstrual cycle disturbances, longer pregnancies, spontaneous abortions, stillbirths, and some developmental effects in offspring have been linked to OP pesticide exposure. Prenatal exposure has been linked to impaired fetal growth and development. The effects of OP exposure on infants and children are at this time currently being researched to come to a conclusive finding [49,76]. Evidence of OP exposure in pregnant mothers are linked to several health effects in the fetus. Some of these effects include delayed mental development, Pervasive developmental disorder (PDD) [16], morphological abnormalities in the cerebral surface [55]. Exposure to OP pesticides were mainly measured in three ways: (1) using dialkyl phosphate (DAP) metabolites collected from urine (2) using pesticide-specific metabolites found in urine and (3) measuring cholinesterase (ChE) and butyryl cholinesterase (BChE) [3]. It was found that high exposure to OP pesticides prenatally (measured by DAP in urine) is associated with lowered IQ scores in 7-year-old children. Higher DAP levels were associated with lower scores on four cognitive areas, with the strongest association in verbal comprehension. A separate study also showed that higher prenatal chlorpyrifos (CPF) exposure was also linked to several brain anomalies. These studies used MRI and compared 20 low CPF exposure children to 20 high CPF exposure children. It was found that although overall brain size did not differ between exposure groups, there were significant areas of the brain that were enlarged in children with high exposure. These enlargements were primarily due to an increase of underlying white matter in the high exposure group. Enlargements were seen bilaterally in the superior temporal, posterior middle temporal, and inferior postcentral gyri, and superior frontal gyrus, straight gyrus, cuneus, and precuneus in the medial views of the right hemisphere [55].

b. Neurotoxic effects:

Neurotoxic effects have also been linked to poisoning with OP pesticides causing four neurotoxic effects in humans: cholinergic syndrome, intermediate syndrome, organophosphate-induced delayed polyneuropathy (OPIDP), and chronic organophosphate-induced neuropsychiatric disorder (COPIND). These syndromes result after acute and chronic exposure to OP pesticides.

Cholinergic syndrome occurs in acute poisonings with OP pesticides and is directly related to levels of AChE activity. Symptoms include miosis, sweating, lacrimation, gastrointestinal symptoms, respiratory difficulties, dyspnea, bradycardia, cyanosis, vomiting, diarrhea, as well as other symptoms. Along with these central effects can be seen and finally seizures, convulsions, coma, respiratory failure. If the person survives the first day of poisoning personality changes can occur, aggressive events, psychotic episodes, disturbances and deficits in memory and attention, as well as other delayed effects. When death occurs, it is most commonly due to respiratory failure from the combination of central and peripheral effects, paralysis of respiratory muscles and depression of the brain respiratory center. For people afflicted with cholinergic syndrome, atropine sulfate combined with an oxime is used to combat the effects of the acute OP poisoning. Diazepam is sometimes also administered in combination with the atropine and oximes [27]. The intermediate syndrome (IMS) appears in the interval between the end of the cholinergic crisis and the onset of OPIDP. Symptoms associated with IMS manifest within 2–96 hours after exposure. The exact etiology, incidence, and risk factors associated with IMS are not clearly understood, but IMS is recognized as a disorder of neuromuscular junctions. IMS occurs when a person has a prolonged and severe inhibition of AChE and has been linked to specific OP pesticides such as methylparathion, dichlorvos, and parathion. Patients present with increasing weakness of facial, neck flexor and respiratory muscles.

OPIDP occurs in a small percentage of cases, roughly two weeks after exposure, where temporary paralysis occurs. This loss of function and ataxia of peripheral nerves and spinal cord is the phenomenon of OPIDP. Once the symptoms begin with shooting pains in both legs, the symptoms continue to worsen for 3–6 months. In the most severe cases quadriplegia has been observed. Treatment only affects sensory nerves, not motor neurons.
which may permanently lose function. The aging and phosphorylation of more than 70% of functional NTE in peripheral nerves is one of the processes involved in OPIDP [40]. Standard treatments for OP poisoning are ineffective for OPIDP.

COPIND occurs without cholinergic symptoms and is not dependent on AChE inhibition. COPIND appears with a delay and is long lasting. Symptoms associated with COPIND include cognitive deficit, mood change, autonomic dysfunction, peripheral neuropathy, and extrapyramidal symptoms. The underlying mechanisms of COPIND have not been determined, but it is hypothesized that withdrawal of OP pesticides after chronic exposure or acute exposure could be a factor [27].

c. Effects on developing animals:
Evidence of exposure to OP pesticides during gestation and early postnatal period have been linked to neurodevelopmental effects in animals, specifically rats. Animals exposed in utero to chlorpyrifos exhibited decreased balance, poorer cliff avoidance, decreased locomotion, delays in maze performance, and increased gait abnormalities. Early gestation is believed to be a critical time period for the neurodevelopmental effects of pesticides. OP's affect the cholinergic system of fetuses, so exposure to chlorpyrifos during critical periods of brain development potentially could cause cellular, synaptic, and neurobehavioral abnormalities in animals [16]. In rats exposed to methyl parathion, studies found reduced AChE activity in all brain regions and subtle alterations in behaviors such as locomotor activity and impaired cage emergence. Organophosphates as whole have been linked to decreases in the length of limbs, head circumference, and slower rates of postnatal weight gain in mice [16].

Biochemical and hormonal changes:
Organophosphorus compounds have many toxicological effects on the body such as:

- Respiratory disorders: OPs caused a central failure of breathing in all animals. The key findings were rapidly progressive bradypnoea leading to apnoea due to loss of respiratory effect.
- Loss of central inspiratory drive due to poisoning has been found [61]. The lack of paralysis of respiratory muscles is also supported by other studies that demonstrated intact diaphragmatic following OP poisoning [60].
- Hepatological disorders: Liver is the organ where activation and detoxification of OP compounds takes place. But they are eliminated primarily through kidneys [1]. Earlier the profile of liver marker enzymes, antioxidant enzymes and essential trace elements were found to be adversely affected after OP intoxication to rats [19]. The histopathological changes observed in human liver observed in a forensic laboratory are: Congestion, Centrilobular necrosis, Fatty changes, Alcoholic hepatitis and Sinusoidal dilatation [64]. At high doses of OP, rats exhibited extreme injury in their liver [64].
- Cardiovascular disorders: Povoa, have reported that OPs induced acute poisoning with myocardial necrosis [52]. Saadeh, reported that there will be an increased in Creatinine kinase and lactate dehydrogenase levels, after OP poisoning [62].
- Cardiac Manifestations: Sinustachycardia, sinus bradycardia, hypertension, hypotension, impaired heart rate and force contraction [29].
- ECG changes: Prolonged QTc interval, ST segment elevation, low amplitude T waves, extrasystole and prolonged PR interval [77].
- Neurological disorders: Neuronal necrosis has been observed in multiple cortical and subcortical regions in experimental rats exposed tolerate acute doses of OP compounds [50].
- OP also leads to a delay in stimulus classification, which in turn depends on attentional resources and the working memory system of the brain, this impairment appears to persist even 6 months after poisoning [7]. Several chronic CNS disturbances due to acute or chronic OP agent poisoning have 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 [24].
- Hormonal imbalance: In late 20th century, several experimental and epidemiological studies regarding hormonal imbalance especially sex hormones leading to adverse developmental outcomes related to pesticide exposure, including foetal death, intrauterine growth restriction, congenital malformations and male / female fertility have been published [18]. Living in rural areas where large amounts of pesticides are applied represents a risk factor for fertility [39].
- Oesophageal effects: Emergent esophago-gastroscopy revealed circumferential hyperthermia, oedema and bleeding throughout esophagus [22].
- Renal impairment: Many studies reviewed by the Ontario College show positive associations 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 [25].
Oxidative stress and Antioxidant status: Studies have shown that OP poisoning is associated with enhanced lipid peroxidation, reduced Glutathione levels and elevated antioxidant status and increased oxidative stress [72,54].

REFERENCES


