Potential Human Health Impacts and Medical Treatment of Acute Poisoning with Organophosphorus Pesticides (OPs): A Review

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Abstract: Organophosphate pesticides (OPs) are compounds that can be detected in human populations as a result of occupational or residential exposure. Despite their occurrence in considerably low levels in humans, their biological effects are hazardous since they interact with enzymes, proteins, receptors and transcription factors. The mechanism of OP poisoning involves inhibition of acetylcholinesterase (AChE) leading to inactivation of the enzyme which has an important role in neurotransmission. AChE inhibition results in the accumulation of acetylcholine at cholinergic receptor sites, producing continuous stimulation of cholinergic fibers throughout the nervous systems. Therefore, OP causes immunomodulatory effects, cancer, neurotoxicity and different infections. During more than five decades, pyridinium oximes have been developed as therapeutic agents used in the medical treatment of poisoning with OP. They act by reactivation of AChE inhibited by OP. However, they vary in their activity in poisoning with pesticides and warfare nerve agents and there is still no universal broad-spectrum oxime capable of protecting against all known OP. In this paper the available information related to health impacts and medical treatment of OP poisoning are reviewed and summarized, and the current recommendations are presented.

Keywords: Organophosphorus Pesticides, Health Impacts, Medical Treatment, Pyridinium Oximes, Atropine

1. Introduction

Pesticides are widely used to prevent or reduce losses of agricultural production by pests to maximize yield which is important to the consumers and the farmers (Oerke and Dehne, 2004; Cooper and Dobson, 2007). Despite their popularity for effective pest control, they are using at tremendous rate in agricultural field which eventually threatening human health. The first exposure to pesticides are farmers when mixing and applying pesticides or working in treated fields and the second exposures are consumers affected from residues on food and in drinking water (Van der Werf, 1996; Wilson and Tisdell, 2001; Pimentel, 2005; Maroni et al., 2006; Soares and Porto, 2009). These activities results accidental poisonings, and can pose major health risks to farmers. Organophosphorus pesticides (OPs) are of major concern among all pesticides because of their higher toxicity to human health. OPs have usually developed as warfare nerve agents such as soman, sarin, tabun, VX and others. In addition, poisoning by OPs pesticide is an important clinical problem in rural regions of the developing world that kills an estimated 200,000 people every year (Jokanović, 2009). Accidental toxification kills far fewer people but is a perceptible dilemma in places where highly toxic OP pesticides are accessible. Fatality rate accounts more than 15% for these toxic OPs where medical management is certainly difficult (Eddleston et al., 2008). Phosphorylation of the serine hydroxyl group in the active site of acetylcholinesterase (AChE) is the main mechanism of OP poisoning which eventually leading to the inactivation of this essential enzyme for neurotransmission. AChE reticence results in the addition of acetylcholine at cholinergic receptor sites, producing constant stimulation of cholinergic fibers throughout the central and peripheral nervous systems. Currently, an arrangement of an antimuscarinic agent, e.g. atropine, AChE reactivator such as one of the recommended pyridinium oximes (pralidoxime, trimedoxime, obidoxime...
and HI-6) and diazepam are used for the treatment of OP poisoning in humans.

This review presented a brief view on the evaluation of possible impacts of OPs into human. The purpose of this paper is to present and discuss common factors affecting exposure to pesticides, health impacts, and medical treatment of acute poisoning with OPs.

2. Human Exposure to Pesticides and Factors Affecting Exposure

Human exposure to pesticides may occur in many ways e.g. occupational exposure, farmers in the field, workers in the pesticide industry, and exterminators of house pests (Van der Werf, 1996; Wilson and Tisdell, 2001; Pimentel, 2005; Maroni et al., 2006; Soares and Porto, 2009, Atreya, 2008; Tarig et al., 2007; Martinez-Valenzuela et al., 2009). Evidently, the greatest exposure notice in workers who mix, load, transport and apply formulated pesticides because of the nature of their work and eventually they are at highest risk for possible acute intoxications (Fenske and Day, 2005). Furthermore, accidental spills of chemicals, leakages, or faulty spraying equipment may also expose people to pesticides. The exposure of workers may significantly increases in the case of violation of pesticide utilization instruction and ignores basic safety guidelines. The poor use of personal protective equipment (PPE) and fundamental sanitation practices such as washing hands after pesticide handling or before eating may also contribute the risk.

The exposure during pesticide handling may be affected by several factors e.g. the form of formulation of pesticide products may affect the extent of exposure (Fenske and Day, 2005). Liquids are prone to splashing and occasionally spillage, resulting in direct skin contact or indirect skin contact through clothing contamination. The particulate dust may generate while being loaded the solids into the application equipment, resulting in exposure to the face and the eyes and also cause respiratory hazards. Packaging patterns of pesticide products can also affect potential exposure to human. The chemical volatility of the product, the perspiration rate of the human body, and the use of personal protective equipment by the users are all may affected by the weather factors such as air temperature and humidity at the time of pesticide application (Fenske and Day, 2005; Gil et al., 2008; Jindal et al., 2007; Gomes et al., 1999). Furthermore, the frequency and duration of handling pesticide both on a seasonal and lifetime basis affects the exposure. In particular, a commercial applicator that normally applies a pesticide for many consecutive days or weeks in a season is more vulnerable than an individual farmer that applies a pesticide once a year (Fenske and Day, 2005).

The exposure of general population to pesticides occurs mainly through dietary intake of food and drinking water contaminated with pesticides, whereas substantial exposure to pesticides can also occur when living close to a workplace that uses pesticides or even when workers bring home contaminated objects (Davis et al., 1992; Jaga and Dharmani, 2003).

3. Health Impacts of OPs

Pesticide is usually the substance used to kill, repel, or control certain forms of plant or animal life that are considered as pests. Pesticides pose a public health concern because of their ubiquitous presence in the living and working environments, and their bioavailability into organisms. Because of the widespread use in agriculture, people are exposed to low levels of OPs pesticide residues through their diets, and to pesticides used in a variety of settings including homes, schools, hospitals, and workplaces and uncertainty still remain regarding possible health effects related to this long term and low levels exposure. The potential impacts of OPs on human health are discussed below-

3.1. Immunomodulatory Effects of Organophosphates in Humans

OPs are widely used throughout the world as insecticides in agriculture and as eradicating agents for termites. However, OPs may pose a major threat on human immune system. OPs can affect both in vivo and in vitro the immune response, including effects on antibody production, IL-2 production, T cell proliferation, decreased CD5 cells, and increases of CD26 cells and autoantibodies, altered Th1/Th2 cytokine profiles, and inhibition of NK cells, lymphokine-activated killer (LAK) cell, and cytotoxic T lymphocytes (CTL) activity. In Tables 1 the current evidence of immune effects of OP pesticides in humans following occupational or environmental exposure are summarized and, were available, the levels of exposure associated with the observed effects are reported. The tables clearly show that available data are incomplete, and contradictory results have been sometimes obtained but in some cases the levels of exposure are lower than those usually considered as source of possible concern. Mechanisms of OP-induced inhibition of the activities of NK cells, LAK cells, and CTLs have been recently reviewed (Li, 2007). Three mechanisms have been suggested by Corsini et al. (2012), (1) OPs impair the granule exocytosis pathway of NK cells, LAK cells, and CTLs by inhibiting the activity of granzymes, and by decreasing the intracellular levels of perforin, granzyme A, and granulysin, which were mediated by inducing degradation of NK cells and by inhibiting the transcription of the mRNAs of perforin, granzyme A, and granulysin. (2) OPs impair the FasL/Fas pathway of NK cells, LAK cells, and CTLs by inhibiting the activity of granzymes, and by decreasing the intracellular levels of perforin, granzyme A, and granulysin, which were mediated by inducing degradation of NK cells and by inhibiting the transcription of the mRNAs of perforin, granzyme A, and granulysin. (3) OPs induce apoptosis of immune cells. In addition, organophosphate insecticides may also exert an immunomodulatory effect both via inhibition of serine hydrolases or other esterases in immune cells, or through oxidative damage to immune organs, or by modulation of signal transduction pathways (Galloway and Handy, 2003).

3.2. Organophosphates and Cancer

Organophosphate pesticides are rated as probable or possible carcinogens, according to the USEPA (USEPA, 2004).
and the IARC (IARC, 1991) classification while several are recognized as carcinogens in humans. They may thus act as complete carcinogens, tumor initiators, and promoters. In a case–control study of children, Soldin et al. (2009) studied the association of acute lymphoblastic leukemia with organophosphate exposure as one of the risk factor. Oxidative stress and DNA damage have been proposed as mechanisms for cancer development. Long-lasting or acute oxidative stress disturbs cell metabolism and is able to produce permanent changes in the structure of proteins, lipids, and DNA. The proteins that are oxidized may lose or enhance their activity. Moreover, the proteins oxidized are able to form aggregates that inhibit the systems responsible for protein degradation and lead to alterations of proteins in the cell. In a pilot study of pesticide applicators and farm workers was conducted to examine the relationship between organophosphate pesticide exposure and oxidative stress and DNA damage (Kisby et al., 2009). In this study organophosphate metabolites were found in urine sample at significantly higher level and reactive oxygen species and reduced levels of glutathione which are markers of oxidative stress and oxidative DNA damage were also observed in lymphocyte cell cultures treated with organophosphates. In a cohort study of 81 agriculture workers changes in erythrocyte antioxidant enzymes were assessed twice during the course of a pesticide spraying season (López et al., 2007). As a consequence of high exposure period, sprayers presented lower levels of superoxide dismutase (SOD) and glutathione reductase as compared to controls. Thus authors hypothesized that lower enzyme activities are the result in structure of proteins, lipids, and DNA. These changes in the structure of proteins, lipids, and DNA may lead to alterations of proteins in the cell. In a pilot study of pesticide applicators and farm workers was conducted to examine the relationship between organophosphate pesticide exposure and oxidative stress and DNA damage (Kisby et al., 2009).

### 3.3. Interaction with Endocrine System

Organophosphorus pesticides (OPs) have been documented to affect the endocrine system in any stage of hormonal regulation, from synthesis to hormone receptor binding (Bretveld et al., 2007), resulting in reproductive and developmental adverse effects. The OP insecticide dichlorvos increases the apoptosis of Leydig cells in the offspring of pregnant rats (Zeng et al., 2009). OPs are capable of interfering with the endocrine function by inhibiting the binding of thyroid hormones to their corresponding receptors. OPs also reduce the metabolism of oestradiol and perturb its normal function by potent inhibition of cytochrome P450 (CYP450) enzymes (Symonds et al., 2006; Trankina et al., 1985), as a result of the binding of the active sulfur atom that arises from desulfuration in phase I metabolism (Hodgson and Rose, 2006). OPs such as chlorpyrifos are also able to inhibit adrenal steroidogenesis, thus affecting the hormonal status (Civen et al., 1977; Walsh et al., 2000).

### 3.4. Neurotoxicity

Exposure to OPs can produce some long-term neurotoxic consequences as a result of acute poisoning and after long-term exposure to subclinical doses of OPs. Irreversible AChE inhibition after acute OP exposure may produce brain damage due to cholinergic neuronal dysfunction and excitotoxicity. Cholinergic neurons damaged by high OPs doses might be responsible for persistent profound neuropsychiatric and neurobehavioral impairments, including memory, cognitive, mental, emotional, motor and sensory deficits (Chen, 2012; Kanavouras et al., 2011; Androutsopoulos et al., 2011). Recent reports suggest an additional mechanism of neurotoxicity due to OP interference with normal neurodevelopment that appears to be independent of the cholinergic effects since they occur at concentrations below those affecting cholinergic transmission (Pope et al., 2005). Chlorpyrifos and diazinon elicit adverse effects on brain development at exposures lower than those required to inhibit AChE, with the adverse effects involving the parent compounds and not their oxon metabolites, which are responsible for AChE inhibition (Jameson et al., 2007). These compounds also affect brain development after fetal and childhood exposures through mechanisms other than cholinergic overstimulation, particularly by targeting pathways involved in normal cell development and alterations in the expression and function of nuclear transcription factors that control cells replications, differentiation and apoptosis (Dam et al., 2003; Slotkin and Seidler, 2007).

### 3.5. Infections

Immunosuppression induced by pesticides may explain the relation with increased infections in humans observed in several studies (Hermanowicz and Kossman, 1984; Dewailly et al., 2000; Dallaire et al., 2004; Sunyer et al., 2010), in occupationally exposed workers at levels not exceeding the concentration of 1 mg/m³ (Hermanowicz and Kossman, 1984). Particularly children are susceptible to immunotoxicity, as the vulnerable period for toxic insults to the developing immune system extends from early gestation to adolescence (Dietert, 2008). There are also some studies addressing the risk of infections associated with pesticide exposure in adults. OP compounds caused the reduction of neutrophil functions (i.e. phagocytosis, respiratory burst, adhesion) accompanied by increase of upper respiratory tract infections (i.e. tonsillitis, pharyngitis, and bronchitis) in the exposed subjects (Hermanowicz and Kossman, 1984; Nakamishi et al., 1985; Wang et al., 2010). OPs are potent acetylcholinesterase inhibitors, OPs are a leading case of self-poisoning in patients due to their widespread use and toxicity. Overstimulation of both nicotinic and muscarinic receptors can compromise the respiratory system, which in combination with OP and carbamates-induced immunosuppression may lead to pneumonia complication, as observed in 26–58% of patients with cholinesterase inhibitor poisoning (Wang et al., 2010).
4. Medical Treatment of Acute Poisoning with Organophosphorus Pesticides

4.1. General Measures

Medical treatment is a very important part of the management of OP poisoning cases. Management includes 4 stages, (1) Initial stabilization of patient by maintaining respiration and other vital signs; (2) reduction of exposure, (3) administration of specific antidote, (4) supportive treatment (WHO, 2007). The initial objective of management is founding of clear airway and adequate ventilation, because in OP poisoning there is respiratory distress secondary to bronchospasm, increase respiratory secretion, pulmonary oedema etc. OP poisoning patient should be removed from exposure source, contaminated clothings are taken away and exposed areas are cleaned with soap and water. Treatment of OP pesticide poisoning should begin with decontamination and resuscitation. Decontamination is important in minimizing the dose of the pesticide absorbed, but precaution must be taken not to contaminate others, such as medical and paramedical workers. In the case of ingestion, lavage can be performed and activated charcoal administered and sometimes stomach wash is given by 1: 5000 potassium permanganate solutions (Jokanović, 2009). During the early stages of treatment, patient should be observed carefully because respiratory arrest may occur. Solvent vehicles and other components of the formulated OP pesticides may obscure the clinical condition that should be taken into consideration (IPCS, 1989). However, ingested organophosphates should be removed by early gastric aspiration and lavage. Gastric lavage is most effective within 30 min of ingestion, but might be still effective up to 4 h post-ingestion, as organophosphates are quickly absorbed from the gastrointestinal tract (World Health Organization, 1986).

Oral activated charcoal may be administered considerably for reducing further absorption of some OP pesticides (World Health Organization, 1986). This recommendation was supported by Peng et al. (2004) who performed a randomized controlled clinical trial including 108 patients aimed to determine the efficacy of hemoperfusion with charcoal in the treatment of dichlorvos poisoning. Peng et al. (2004) also concluded that the rapid fall in blood dichlorvos level and the dramatic clinical response advocate that hemoperfusion with charcoal is effective in the treatment of acute organophosphate pesticide, dichlorvos poisoning. But the contrast of these results also reported by Eddleston et al. (2005), they conducted a randomized controlled trial of single and multiple doses of activated charcoal in Sri Lanka that failed to find a significant benefit of either regimen over placebo in more than 1000 patients poisoned with pesticides. In addition, Eddleston et al. (2008) also performed an open-label, parallel group, randomized, controlled trial in three Sri Lankan hospitals which aimed to determine whether routine treatment with multiple-dose activated charcoal offers benefit compared with no charcoal. Besides, there were no differences in mortality between patients treated with or no charcoal among 2338 patients who ingested pesticides (1310 cases of poisoning with OP pesticides). They also concluded that they cannot recommend the routine use of multiple dose activated charcoals in OP pesticides poisoning and suggest that further studies of early charcoal administration might be useful.

4.2. Specific Therapy

4.2.1. Atropine

Atropine sulphate in association with an oxime has been used in traditional therapy for OP intoxications including insecticides. Atropine can mitigate the following symptoms of OP poisoning: sweating, salivation, rhinorrhoea, lacrimation, nausea, vomiting and diarrhea, and can help control of bradycardia and circulatory depressions, dilating the bronchi and abolishing bronchorrhoea. According to IPCS (2002) in severe OP poisoning total dose of atropine given during 5 weeks of treatment can be as high as 30,000 mg.

4.2.2. Pyridinium Oximes

Pyridinium oximes are useful against OP-inhibited AChE in the peripheral nervous system, but have a limited penetration across the blood–brain obstacle due to their pharmacokinetic profile and the presence of quaternary nitrogen atom(s) in their structure. Among the many classes of oximes investigated so far, those with clinical application can be separated in two groups—the monopyridinium and bispyridinium oximes. Currently, the only used monopyridinium oxime is pralidoxime (PAM-2), while the most significant bispyridinium oximes comprise: trimedoxime (TMB-4), obidoxime (LuH-6, Toxogonin) and asoxime (HI-6).

Pralidoxime administered to human bodies at a dose of 10 mg/kg by intramuscular route, produced a plasma concentration of >4 mg/L within 5–10 min and maintained levels above this threshold for an hour (Sidell and Groff, 1971). Adverse effects of PAM-2 iodide in the human bodies include dizziness, blurred vision, occasional diplopia, impaired accommodation, nausea and headache (Sidell and Groff, 1971). The PAM-2 iodide with atropine and diazepam used in the treatment of the victims of Tokyo sarin attack victims in 1995 was extremely favorable (Stojiljkovi´c and Jokanović, 2005). However, PAM-2 should not be suggested as the drug of choice in poisoning with warfare nerve agents due to its lack of efficacy against tabun and soman (Kassa, 2005).

Obidoxime administered to human bodies by intramuscular route obidoxime 5 mg/kg produced a plasma concentration >4 mg/L, from 5 min after injection to 3 h (Sidell and Groff, 1970). Adverse effects of obidoxime in male volunteers were reported as pallor, nausea, burning sensation, headache, generalized weakness, and sore throat (Simon and Pickering, 1976; Eyer, 2003; Marrs and Vale, 2006). Due to high doses of obidoxime (several grams per day) in severely OP poisoned patients, hepatotoxic effects were occasionally observed including increased serum transaminases, jaundice and cholestasis (Eyer, 2003).
Asoxime (HI-6) administered to human bodies dosed at either 250 mg or 500mg by intramuscular route reached plasma concentrations >4 mg/L in 4–6 min. This concentration was continued for 125 min following the lower dose (250 mg) and 200 min following the higher dose (500 mg) (Kušić et al., 1985, 1991). A clinical study was conducted on 22 healthy human volunteers producing no adverse effects when HI-6 was given in doses up to 500mg by oral route (Jovanović et al., 1990). HI-6 was considered to be an effective antidote (in combination with atropine and diazepam) in treatment of patients poisoned with OP insecticides, but it has disadvantage compared to other available oximes is its lack of stability in aqueous solutions (Kušić et al., 1991).

It is vital to note that oximes are not effective for improvement of outcomes if the patient reduces severe complications such as aspiration pneumonia or hypoxic brain injury before treatment. Such complications occur with fast-acting pesticides such as parathion and dichlorvos (Eddleston et al., 2008).

5. Conclusions and Recommendations

Though organophosphorus pesticides play an important role in agricultural production by killing pests, they have numerous negative effects on human health like immunotoxicity, cancer, neurotoxicity, endocrine disruption, and infections etc. Medical management of acute OP pesticide poisoning in humans includes general (decontamination and supportive measures) and specific treatment with atropine and oximes (pralidoxime, trimedoxime, obidoxime, and HI-6). Though about a half of the century has passed since the introduction of the antidotes to medical treatment of patients poisoned with OP compounds in developed countries, the accessibility of these treatment is very limited in developing countries. So, it is urgent necessary to implement the following recommendations:

- to monitor strictly occupational and residential pesticide exposure
- to educate farmers about the proper use of pesticides
- to ensure the proper uniforms of farmers during the mixing and application of pesticides
- to create awareness about the toxicity of pesticides
- to develop and improve exposure assessment methods
- to perform properly and carefully designed clinical trials to assess the efficacy of different medical treatment of pesticide poisoning.

Table 1. Immunomodulatory effects of organophosphate pesticides in humans.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Trend</th>
<th>Effect</th>
<th>Type of exposure</th>
<th>Dose of exposure</th>
<th>Author (year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpyriphos</td>
<td>Increase</td>
<td>Atopy and antibiotic sensitivity</td>
<td>Occupational</td>
<td>Surface wipes: &lt;10 to 2900 ppm 5 months after application.</td>
<td>Thrasher et al. (1993)</td>
</tr>
<tr>
<td></td>
<td>Decrease</td>
<td>CD5, proliferative response to mitogens CD26, autoantibodies and autoimmune</td>
<td>Environmental</td>
<td>Environmental concentration (puddles and vegetable): 0.013 and 0.074 ppm</td>
<td>Thrasher et al. (2002), Thrasher et al. (1993)</td>
</tr>
<tr>
<td>OP</td>
<td>Decrease</td>
<td>Asthma and atopic reaction</td>
<td>Occupational</td>
<td>10 nM–10 µM</td>
<td>Garry et al. (1994)</td>
</tr>
<tr>
<td></td>
<td>Decrease</td>
<td>NK and CTL cells activity</td>
<td>In vitro</td>
<td>16.5 ± 0.36 year of exposure</td>
<td>Wilson et al. (2004)</td>
</tr>
<tr>
<td></td>
<td>Decrease</td>
<td>CD5 Cells, NK cells, LAK cells, CTLs</td>
<td>Human</td>
<td>OPs at concentrations ranging from 10 to 200 nM; Ziram at concentrations of 2.5 µM and Maneb at concentrations of 1–10 µM</td>
<td>Li (2007)</td>
</tr>
<tr>
<td>OP by products of sarin (DIMP and DEMP)</td>
<td>Increase</td>
<td>Infections of the upper respiratory tract</td>
<td>Occupational</td>
<td>Effective dose (IC50) DDVP: 0.55 mM DMTA: 1.423 mM, ESP Acephate: 17.75 mM</td>
<td>Hermanowicz et al. (1984)</td>
</tr>
<tr>
<td></td>
<td>Decrease</td>
<td>NK and CTL activity</td>
<td>Human (accidental poisoning)</td>
<td>The concentration of DIMP or DEMP for human PBL were 0.125, 250 or 500 ppm</td>
<td>Li et al. (2000)</td>
</tr>
</tbody>
</table>


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