LEADING ARTICLE

Toxicity due to organophosphorus compounds: what about chronic exposure?

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Summary The inappropriate use of toxic chemicals is common in developing countries, where it leads to excessive exposure and high risks of unintentional poisoning. The risks are particularly high with the pesticides used in agriculture, where poor rural populations live and work in close proximity to these compounds, which are often stored in and around the home. It is estimated that 99% of all deaths from pesticide poisoning occur in developing countries. Whilst the acute toxicity of pesticides has been well documented, there is still relatively little known of the effects on health of chronic pesticide exposure. Organophosphate insecticides have been extensively used in agriculture in developing countries, with little protection for the communities and individuals thus exposed. Given the indisputable chronic exposure of vulnerable groups to organophosphate compounds, including pregnant women, the fetus and young children, the potential for widespread adverse effects is considerable. Thus, whilst there is some evidence that chronic exposure may have adverse effects on health, there is an urgent need for high-quality observational and interventional studies of both occupational and environmental exposure to these compounds.

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1. Introduction

Unintentional poisonings kill an estimated 355,000 people each year (WHO, 2003). Two-thirds of these deaths occur in developing countries, where such poisoning is strongly associated with excessive exposure to, and inappropriate use of, toxic chemicals. In many such settings, the toxic chemicals may be emitted directly into soil, air and water—from industrial processes, pulp and paper plants, tanning operations, mining and unsustainable forms of agriculture—at levels or rates well in excess of those tolerable to human health (United Nations Development Programme, 1998; World Bank, 2002; Yáñez et al., 2002). The Organisation for Economic Co-operation and Development (OECD) has estimated that by the year 2020 nearly one-third of the world’s chemical production will take place in non-OECD countries and that global output will be 85% higher than it was in 1995. The shift of chemical production to poor countries may increase related health and environmental risks (OECD, 2001).

There are many pesticides, with thousands of trade names. Two-thirds of their total use is in agriculture. The WHO report on pesticides in agriculture estimated 220,000 deaths due to pesticide poisoning in 1990; 99% of these were in the developing world and 20,000 were unintentional (WHO, 1990). Chronic pesticide exposure is often a problem in occupational settings, particularly among poor rural populations, where men, women and children all work and live in close proximity to fields on which chemicals are applied and stored (Food and Agriculture Organization of the United Nations/United Nations Environment Programme/WHO, 2004; World Bank, 2002). The pesticides most commonly used in agriculture are organophosphorus compounds (OPCs). There are...
more than 100 different OPCs, and poisoning due to these chemicals, both intentional and unintentional, is a worldwide health problem; unintentional poisoning may disproportionately affect infants and children (Food and Agriculture Organization of the United Nations/United Nations Environment Programme/WHO, 2004).

2. Acute toxicity

Organophosphorus compounds exert acute systemic toxicity by inhibiting the enzyme acetylcholinesterase (AChE) through a process of phosphorylation. This leads to an accumulation of the neurotransmitter acetylcholine at nerve endings, which produces the common signs of OPC intoxication. The harmful effects of acute exposure manifest as an acute cholinergic crisis, an intermediate syndrome consisting of paralysis of the neck, proximal limb and respiratory muscles 24 to 96 h after the cholinergic crisis, and a delayed onset distal polyneuropathy 2–3 weeks after poisoning. Restoration of AChE activity occurs by de-novo biosynthesis of new enzyme, slow spontaneous dephosphorylation of the inhibited enzyme, and as a result of treatment with oximes. The rate and extent of dephosphorylation of the inhibited enzyme and its subsequent reactivation depends on the exact structure of the OPC residue and the treatment given. Besides their inhibitory effects on AChE, there is increasing evidence that OPCs also induce oxidative stress through generation of free oxygen radicals, leading to lipid peroxidation and DNA damage (Bagchi et al., 1995; Gutierrez et al., 2000; Vidyasagar et al., 2004). And, although administration of atropine and oximes to patients with acute OPC poisoning has led to increases in both serum and erythrocyte ChE levels, these treatments failed to have a significant effect on the oxidant status (Vidyasagar et al., 2004). However, there is as yet no clear indication that oxidative stress has any pathogenic role in OPC poisoning.

Animal studies have shown that the fetus and the very young are more susceptible to damage by acute exposure to OPC than the adult, possibly because of their immature microsomal enzyme system and greater permeability of the blood–brain barrier; but teratogenic effects seem to be rare (Gallo and Lawryk, 1991; WHO, 1986). Parathion, an OPC, was toxic to the rat fetus, causing pre-natal and post-natal death of the young and reduced weight gain in the surviving weanlings. AChE activities in brain and liver tissues from maternal and fetal rats showed that enzyme activity in both the fetal liver and brain was more inhibited than in the maternal counterpart (Taha and Gray, 1993). The extent and effects of toxicity due to acute OPC poisoning are well documented in terms of clinical syndromes, assessment of severity and complications (Edleston et al., 2005; Senanya et al., 1993), and treatment (Buckley et al., 2005; de Silva et al., 1992), and are the subjects of extensive ongoing research.

3. Chronic toxicity

There is a paucity of data on the possible deleterious effects of chronic exposure to OPCs in occupational and/or environmental settings. In general, the literature brings out three types of ‘non-acute’ OPC poisoning: occupational exposure with reductions in ChE levels; occupational exposure with no reduction in ChE levels; and environmental exposure. However, the relationships between chronic exposure, ChE inhibition and symptoms do not, as yet, seem to be well established.

Available evidence suggests that there is a possibility of adverse effects occurring below OPC concentrations that are generally considered to be safe based on measurements of ChE inhibition; i.e. these effects are not clearly related to the inhibition of cholinesterases (Ames et al., 1989; Popendorf, 1990; Salvi et al., 2003; Singh and Sharma, 2000). Studies on health hazards to agricultural workers who handle, store and use OPC pesticides have documented a range of non-specific self-reported symptoms that have been attributed to chronic exposure. These include: burning or prickling of the skin; tingling or numbness of hands and face; muscular twitching or cramps in the face, neck, arms and legs; respiratory symptoms, including chest pain, cough, runny nose, wheezing, shortness of breath, irritation of the throat; excessive sweating; nausea, vomiting, diarrhoea; excessive salivation; abdominal pain; lacrimation and irritation of the eyes; difficulty in seeing; restlessness; difficulty in falling asleep; trembling of hands; and irritability (Ames et al., 1989; Ohayo-Mitoko et al., 2000). An increased prevalence of symptoms was found at ChE activities generally considered to be non-adverse (Ohayo-Mitoko et al., 2000). However, detailed, long-term studies of occupational or environmental exposures to OPC are needed to distinguish the effects of the active OPC from the solvent or other components of the OPC. Subtle abnormalities on neurological examination, such as impaired two-point discrimination and vibration sensation, have also been reported in workers chronically exposed to OPCs (Beach et al., 1996; Stokes et al., 1995). More objective investigations into the effects of chronic OPC exposure on nerve conduction and neuromuscular transmission are inconclusive; some report evidence of nerve abnormalities during occupational exposure (Drenth et al., 1972; Stalberg et al., 1978) while others do not (Engel et al., 1998; Misra et al., 1988). A recent study from Sri Lanka has shown inhibition of AChE enzyme activity and impairment of sensory and motor nerve conduction due to long-term, low-level exposure to OPC (Peiris-John et al., 2002). Evidence of toxicity was found not only among the farmers who directly handled (sprayed) OPCs, but also among those employed in inland fisheries living within a 25 km radius of the cultivated land, who were not directly exposed.

4. Neurobehavioural effects in chronic toxicity

Chronic exposure to OPC has been associated with impaired neurobehavioural performance in some, but not all, epidemiological studies (Eyer, 1995; Ray and Richards, 2001). Chronic organophosphate-induced neuropsychiatric disorders (COPIND) occur without cholinergic symptoms, and although the underlying mechanisms are not established, they do not seem dependent on AChE inhibition (Brown and Brix, 1998; Prendergast et al., 1998; Ray and Richards, 2001; Singh and Sharma, 2000). Clinical features reported include: anxiety disorder; depression; psychotic symptoms;
Chronic exposure to organophosphorus compounds (OPCs) can cause health problems, and although there is the potential for widespread adverse effects, very little is yet known about the problem. The implications are particularly relevant for developing countries given their reliance on OPC-based pesticides and indiscriminate pesticide use in agriculture. Vulnerable groups in society, especially pregnant mothers (and through them the fetus and newborn) and children, could be chronically exposed to OPC due to environmental pollution, making this an area in which high-quality, careful, observational and interventional studies are urgently required.

Conflicts of interest
The authors have no conflicts of interest concerning the work reported in this paper.

References
Ames, R.G., Brown, S.H., Menge, D.C., Kahn, E., Stratton, J.W., 1995. Various clinical features of organophosphate syndrome, which led to the, so far unproved, hypothesis that the illness was caused by chronic exposure to chemical agents with similar effects to OPCs (Gronseth, 2005). Despite these reports of impaired neurobehavioural patterns following chronic exposure to OPC, other reports indicate that asymptomatic exposure to OPC is not connected with an increasing risk of delayed or permanent neuropsychopathological effects (Yer, 1995).

5. Effects of chronic exposure on fetal and childhood health
Studies carried out employing chronic exposure of animals to low doses of the OPC Dursban (chlorpyrifos) during pregnancy or just after birth showed a reduction in the manufacture of DNA and the number of cells in the brain of the fetus and the newborn (Chakraborti et al., 1993). This suggests that the nervous system of the fetus and the very young is several-fold more susceptible than the nervous system of a mature adult to such low-dose exposure (the fetus and the very young are more susceptible than adults to damage by acute exposure to OPC as well). Some OPCs such as chlorpyrifos appear to produce behavioural effects in adult rats after neonatal exposure to levels that have no such effect on adults (Dan et al., 2000; Jett et al., 2001; Levin et al., 2001). The extrapolation of data obtained from animal studies to humans is not always accurate, and there is currently inadequate information from epidemiological studies to enable any firm conclusions to be drawn regarding effects of chronic exposure to OPC on human fetal and childhood health. There is speculation, however, that chronic, low-level exposure to chlorpyrifos early in life may adversely affect the nervous system later and have negative effects on learning and behavioural patterns in children (Ekenazi et al., 1999). In a recent study carried out in Bhopal, India, samples of breast milk were obtained from 12 non-employed mothers aged between 19 and 45 years and assayed for OPC residues (Sanghi et al., 2003). Samples were found to contain an average of 0.23 mg chlorpyrifos and 0.043 mg malathion per litre of milk, showing that contaminated breast milk may well be a means of "vertical" transmission of OPCs.

6. Mechanisms of chronic toxicity
Chronic toxicity to OPCs may be related to the rate of regeneration of AChE and the speed at which pesticide metabolites are hydrolysed and eliminated from the body. This "fast" or "slow" enzymatic hydrolysis status seems to be determined by gene polymorphisms of hydrolases such as paraoxonase (Lee et al., 2003). However, in some situations where there is chronic exposure to OPC, there seems to be poor correlation between evidence of toxicity and the degree of AChE inhibition (Ray and Richards, 2001; Singh and Sharma, 2000). It may well be that toxicity in these situations is mediated more by other mechanisms, such as oxidative stress through OPC-induced generation of free oxygen radicals leading to lipid peroxidation (Bebe and Panemangalore, 2003; Gultekin et al., 2000), rather than inhibition of AChE.

7. Conclusion
There is some evidence that chronic exposure to pesticides can cause health problems, and although there is the potential for widespread adverse effects, very little is yet known about the problem. The implications are particularly relevant for developing countries given their reliance on OPC-based pesticides and indiscriminate pesticide use in agriculture. Vulnerable groups in society, especially pregnant mothers (and through them the fetus and newborns), and children, could be chronically exposed to OPC due to environmental pollution, making this an area in which high-quality, careful, observational and interventional studies are urgently required.

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References


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