Recognition and management of organophosphate poisoning

INTRODUCTION
Pesticide poisoning is a common under-diagnosed illness. Despite recommendations, health care providers generally receive a very limited amount of training in occupational and environmental health, and in pesticide-related illnesses, in particular.

TOXICOLOGY
Organophosphates cause toxicity primarily by phosphorylation of the acetylcholinesterase (AChE) at nerve endings. The result is a loss of availability of AChE so that the effector organ becomes overstimulated by the excess acetylcholine (Ach, the impulse transmitting substance) in the nerve ending. At sufficient dosage, loss of enzyme function allows accumulation of Ach peripherally at cholinergic neuroeffector junctions (muscarine effects), skeletal nerve-muscle junctions and autonomic ganglia (nicotinic effects) as well as centrally. At cholinergic nerve junctions with smooth muscle and gland cells, high Ach concentration causes muscle contraction and secretion, respectively. At skeletal muscle junctions, excess Ach may be excitatory (cause muscle twitching), but also may weaken or paralyse the cell by depolarizing the end-plate. In the CNS, high Ach concentrations cause sensory and behavioural disturbances, incoordination, depressed motor function, and respiratory depression. Increased pulmonary secretions coupled with respiratory failure are the usual causes of death from organophosphate poisoning. Recovery depends ultimately on generation of new enzyme in all critical tissues.

Organophosphates are efficiently absorbed by inhalation, ingestion and skin penetration. To some degree, the occurrence of poisoning depends on the rate at which the pesticide is absorbed. Breakdown occurs chiefly by hydrolysis in the liver; rates of hydrolysis vary widely from one compound to another. In the case of certain organophosphates whose breakdown is relatively slow, significant temporary storage in body fat may occur resulting in delayed toxicity due to late release.

SIGNS AND SYMPTOMS OF POISONING
Symptoms of acute organophosphate poisoning develop during or after exposure, within minutes to hours, depending on the method of contact. Exposure by inhalation results in the fastest appearance of toxic symptoms, followed by the gastrointestinal route and finally the dermal route. All signs and symptoms are cholinergic in nature and affect muscarinic, nicotinic and central nervous system receptors. The critical symptoms in management are the respiratory symptoms. Sufficient muscular fasciculations and weakness are often observed as to require respiratory support; respiratory arrest can occur suddenly. Likewise, bronchorrhea and bronchospasm may often impede efforts at adequate oxygenation of the patient.

Bronchospasm and bronchorrhea can occur, producing tightness in the chest, wheezing, productive cough and pulmonary edema. A life threatening severity of poisoning is signified by loss of consciousness, incontinence, convulsions and respiratory depression. The primary cause of death is respiratory failure, and there usually is a secondary cardiovascular component. The classic cardiovascular sign is bradycardia that can progress to sinus arrest. However, this may be superseded by tachycardia and hypertension from nicotinic (sympathetic ganglia) stimulation. Toxic myocardopathy has been a prominent feature of some severe organophosphate poisonings.

Some of the most common reported early symptoms include headache, nausea, dizziness and hypersecretion, the latter of which is manifested by sweating, salivation, lacrimation and rhinorrhea. Muscle twitching, weakness, tremor, incoordination, vomiting, abdominal cramps and diarrhea all signal worsening of the poisoned state. Miosis is often a helpful diagnostic sign and the patient may report blurred and/or dark vision. Anxiety and restlessness are prominent, as are a few reports of choreiform movements. Psychiatric symptoms including depression, memory loss and confusion have been reported. Toxic psychosis, manifested as confusion or bizarre behaviour, has been misdiagnosed as alcohol intoxication.

A number of nonspecific laboratory findings may be present in an individual with acute poisoning including leukocytosis, proteinuria, glucosuria and haemoconcentration.

OPIDN: Rarely, certain organophosphates have caused a different kind of neurotoxicity consisting of damage to...
the afferent fibres of peripheral and central nerves with associated inhibition of ‘neuropathy target esterase’ (NTE). This delayed syndrome has been termed organophosphate-induced delayed neuropathy (OPIDN), and is manifested chiefly by weakness or paralysis and paresthesia of the extremities. OPIDN predominantly affects the legs and may persist for weeks to years. These rare occurrences have been found shortly after an acute and often massive exposure, but in some cases, symptoms have persisted for months to years. Only a few of the many organophosphates used as pesticides have been implicated as causes of delayed neuropathy in humans.

**Intermediate Syndrome:** Occurs after resolution of the acute cholinergic crisis, generally 24–96 hours after exposure. It is characterized by acute respiratory paresis and muscular weakness, primarily in the facial, neck and proximal limb muscles. In addition, it is often accompanied by cranial nerve palsies and depressed tendon reflexes. Like OPIDN, this syndrome lacks muscarinic symptomatology, and appears to result from a combined pre-and post-synaptic dysfunction of neuromuscular transmission. Symptoms do not respond well to atropine and oximes; therefore treatment is mainly supportive. The most common compounds involved in this syndrome are methyl parathion, fenthion and dimethoate.

**Confirmation of Poisoning**
If poisoning is probable, treat the patient immediately. DO NOT wait for laboratory confirmation.

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**A. Cholinesterase**
Blood samples should be drawn to measure plasma pseudocholinesterase and red blood cell acetylcholinesterase (AChE) levels. Depressions of plasma pseudocholinesterase and/or RBC AChE enzyme activities are generally available biochemical indicators of excessive organophosphate absorption. Certain organophosphates may selectively inhibit either plasma pseudocholinesterase or RBC AChE. A minimum amount of organophosphate must be absorbed to depress blood cholinesterase activities, but enzyme activities, especially plasma pseudocholinesterase, may be lowered by dosages considerably less than are required to cause symptomatic poisoning. The enzyme depression is usually apparent within a few minutes or hours of significant absorption of organophosphate. Depression of the plasma enzyme generally persists several days to a few weeks. The RBC enzyme activity may not reach its minimum for several days, and usually remains depressed longer, sometimes 1–3 months, until new enzyme replaces that inactivated by organophosphate.

RBC AChE is called ‘true’ cholinesterase, since it is the same enzyme present in nerve endings and its activity more closely parallels that in the nervous system than plasma pseudocholinesterase, particularly in the time course of recovery, after inhibition. There is considerable variability in cholinesterase activity in unexposed persons, so that reports of results relative to ‘normal’ are meaningless.

In certain conditions, the activities of plasma and RBC cholinesterase are depressed in the absence of chemi-
cal inhibition. About 3% of individuals have a genetically determined low level (trait) of plasma pseudocholinesterase, but not RBC AChE. They have prolonged muscular paralysis after administration of succinylcholine (a muscle-paralysing drug often administered in theatre) and other neuromuscular blocking agents that are normally metabolized by plasma pseudocholinesterase, but they are not more susceptible to cholinesterase-inhibiting pesticides.

Plasma pseudocholinesterase will not be a reliable indicator of exposure or poisoning in these individuals, but RBC AChE will remain so.

Plasma pseudocholinesterase production may also be lowered extensive enough to impair the production of proteins such as albumin as a result of:
1. Liver disease (hepatitis, cirrhosis, malnutrition, chronic alcoholism) and dermatomyositis,
2. A number of toxicants, notably cocaine, carbon disulphide, benzaalkonium salts, organic mercury compounds, ciguatoxins and solanines and
3. Early pregnancy, birth control pills and metoclopramide.

Albumin-losing conditions, such as nephrotic syndrome, on the other hand, may be accompanied by elevated levels of plasma pseudocholinesterase as a result of increased hepatic protein synthesis.

RBC AChE is less likely than the plasma enzyme to be affected by factors other than organophosphates. The only medical conditions known to influence RBC AChE are those associated with reticuloctysis, such as recovery from haemorrhage, pernicious anaemia and some other anaemias.

### Classification of poisoning

<table>
<thead>
<tr>
<th>Enzyme activity</th>
<th>Classification of poisoning</th>
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<tbody>
<tr>
<td>20–50%</td>
<td>Mild</td>
</tr>
<tr>
<td>10–20%</td>
<td>Moderate</td>
</tr>
<tr>
<td>&lt;10%</td>
<td>Severe</td>
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The status of the patient should be monitored by repeated analysis of the plasma pseudocholinesterase and the RBC AChE; the inhibition of the activities of the 2 enzymes is a good indicator of the severity of organophosphate poisoning.

Note: Carbamate poisoning only inhibit the RBC AChE; the organophosphate chlorpyrifos preferentially depresses plasma pseudocholinesterase without any significant depression of RBC AChE.

There are 2 circumstances in which cholinesterase determinations may be useful:
1. Routine biological monitoring of exposure to organophosphates; and
2. Diagnosis of acute poisoning by organophosphates.

In each case, comparison of the current level to a pre-exposure baseline level is helpful, and for biological monitoring, it is essential. Biological monitoring of exposure consists of determination of pre-exposure baseline levels followed by periodic determinations in intervals based upon the frequency and nature of exposure. If only one test is performed, RBC AChE should be monitored since it is more specific for organophosphate pesticides and is an indicator of cumulative absorption of organophosphate over a relatively long period of time. Plasma pseudocholinesterase is more immediately responsive to inhibition by acute doses and may be preferentially inhibited by some organophosphates such as chlorpyrifos.

The appearance of symptoms is more dependent upon the rate of inactivation of cholinesterase than the absolute level of activity reached, e.g. workers may reach a cholinesterase level of 40% of baseline (60% inhibition) over the course of a number of weeks without experiencing symptoms, but a previously unexposed person may develop symptoms at a level of 70% of baseline activity (30% inhibition) following acute exposure.

An individual’s baseline RBC AChE activity may vary up to 22% from day to day when measured by the same method by the same laboratory. Therefore, 25–30% inhibition (70–75% of baseline) during periodic monitoring can be taken as a warning level of a biological response to chronic exposure to organophosphate pesticides, approaching levels likely to produce intoxication. Removal of workers at this level and prevention of further exposure until levels return to approximately baseline is likely to prevent the development of clinical signs and symptoms of toxicity. Examination of the workplace situation leading to this level of depression is indicated.

Severe poisoning is usually accompanied by cholinesterase levels well below normal for the laboratory. However, patients with mild or moderate poisoning often have cholinesterase levels reported as equivocal, normal or even above normal. The diagnosis can be confirmed retrospectively by periodic i.e. weekly or biweekly determination of cholinesterase until levels fluctuate by no more than 30%. If the average level at this time – the ‘retrospective baseline’ – is more than 30% higher than the level at the time of the illness, exposure to cholinesterase-inhibiting pesticides was almost certainly present, and the illness may have been due to that exposure. The rate of recovery of RBC AChE, in the absence of treatment with pralidoxime and of further exposure, depends upon the rate of formation of new red cells, which is about 1% per day. RBC AChE levels will reach a plateau in about 60–70 days and plasma pseudocholinesterase in 30–50 days.

### B. Intact pesticides and metabolites

Unlike to be helpful in acute intoxication or biological
monitoring due to lack of specificity and instability. Measurement of p-nitrophenol in urine can be useful for monitoring exposure to parathion and 1-naphthol has been used to monitor exposure to carbaryl.

C. Neurotoxic Esterase
Not available commercially.

Differential diagnosis
Acute viral influenza, asthma, respiratory infections, gastroenteritis, psychological dysfunction, heatstroke, heat exhaustion, acute cerebrovascular accidents and acute symmetric polyneuropathy (OIDN).

Treatment
Caution: Persons attending the victim should avoid direct contact with heavily contaminated clothing and vomitus. Wear rubber gloves while washing pesticide from skin and hair. Vinyl gloves provide no protection.
1. Airway protection.
4. Pralidoxime (Protopam, 2-PAM): Before administration of pralidoxime, draw a blood sample for cholinesterase analysis, since pralidoxime tends to reverse the cholinesterase depression. Note: pralidoxime is of limited value and may actually be hazardous in poisonings by the cholinesterase-inhibiting carbamate compounds.
5. Skin decontamination.
7. Observation: Observe the patient closely for at least 72 hours to ensure that symptoms (sweating, visual disturbances, vomiting, diarrhea, chest and abdominal distress and sometimes pulmonary edema) do not recur as atropinization is withdrawn. In very severe poisonings by ingested organophosphates, particularly the more lipophylic and slowly hydrolysed compounds, metabolic disposition of toxicant may require as many as 5–14 days.
8. Furosemide may be considered if pulmonary edema persists in the lungs even after full atropinization. It should not be used until the maximum benefit of atropine has been realized.
10. Hydrocarbon aspiration may complicate poisonings that involve ingestion of liquid concentrates of organophosphate pesticides. Pulmonary edema and poor oxygenation in these cases will not respond to atropine and should be treated as a case of acute respiratory distress syndrome.
11. Cardiopulmonary monitoring: Monitor cardiac status by continuous ECG recording – some organophosphates have significant cardiac toxicity.
12. Seizure control: Rarely, in severe organophosphate poisonings, convulsions occur despite therapy with atropine and pralidoxime. Insure that causes unrelated to pesticide toxicity are not responsible e.g. head trauma, cerebral anoxia or mixed poisoning. Drugs of first choice for initial controlling convulsions are the benzodiazepines (diazepam or lorazepam).
13. Contra-indications: The following drugs are contra-indicated in nearly all organophosphate poisoning cases: morphine, succinylcholine, theophylline, phenothiazine and reserpine. Adrenergic amines should be given only if there is a specific indication such as marked hypotension.
14. Re-exposures: Persons who have been clinically poisoned by organophosphate pesticides should not be re-exposed to cholinesterase-inhibiting chemicals until symptoms and signs have resolved completely and blood cholinesterase activities have returned to at least 80% of pre-poisoning levels. If blood cholinesterase was not measured prior to poisoning, blood enzyme activities should reach at least minimum normal levels before the patient is returned to a pesticide-contaminated environment.
15. DO NOT administer atropine or pralidoxine prophylactically to workers exposed to organophosphate pesticides. Prophylactic dosage with either atropine or pralidoxine may mask early signs and symptoms of organophosphate poisoning and thus allow the worker to continue exposure and possibly progress to more severe poisoning. Atropine itself may enhance the health hazards of the agricultural work setting: impaired heat loss due to reduced sweating and impaired ability to operate mechanical equipment due to blurred vision. This can be caused by midriasis, one of the effects of atropine.

Prognosis
If treatment of organophosphate or carbamate poisoning is initiated before hypoxia results in tissue damage, antidotal therapy and respiratory support should ensure complete recovery, even in the most severe cases. Persistence of manifestations beyond 24 hours indicated the possibility of continued absorption of pesticide and the need to carefully consider and examine the skin, fingernails, eyes and gastrointestinal tract as possible reservoirs.

Reference

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