Poisoning with organophosphates

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In a recent article in this journal [1] I discussed the question of poisoning in South Sudan in an attempt to generate information about the size of the problem. As I pointed out from my experience in Uganda I was concerned about the occurrence of, and mortality from, poisoning with organophosphates. Seventy-one cases of poisoning from organophosphates were reported from forty hospitals and health centres over a six months' period with a 27% mortality. No other agent was associated with a death in this series (Table 1).

Extrapolating these data to the whole country this could reflect 1,250 – 2,500 deaths per year. Worldwide there are thought to be around one million poisonings with a significant mortality. An estimate of mortality from self-poisoning from organophosphates in developing countries is around 200,000 each year [2]. Another study [3] from two hospitals in Kampala, Uganda, over a six months' period in 2005 reported 276 patients but, unlike my review, included patients poisoned with alcohol: 42.4% of patients were poisoned with "agrochemicals". The overall mortality was low at 1.4%.

Table 1. Reports of poisoning in Uganda over six months from 40 health units

Drugs / chemicals	Age up to 10 years		Age over 10 years	
	Number (%)	Deaths	Number (%)	Deaths (%)
Aspirin	1(3%)	0	2 (2%)	0
Batteries	2 (5%)	0	2 (2%)	0
Chloroquine	0	0	3 (3%)	0
Chlorpheniramine	0	0	1 (1%)	0
Diazepam	0	0	2 (2%)	0
Herbicide	0	0	1 (1%)	0
Kerosene	21 (55%)	0	1 (1%)	0
Organophosphate	8 (21%)	0	63 (66%)	19 (30%)
Paracetamol	4 (11%)	0	4 (4%)	0
Rat poison	1 (3%)	0	1 (1%)	0
Unknown	1 (3%)	0	15 (16%)	0
Totals	38	0	95	19 (20%)

What are organophosphates?

These compounds were first produced in the early 1800's by the reaction between alcohol and phosphoric acid. There are two main chemical groups. The phosphorothioates (P=S) which include malathion, parathion, chlorpyrifos, diazinon, disulfoton, phosmet, fenitrothion and the phosphates (P=O) which include dichlorvos and trichlorfon.

What is their toxic action?

They are easily absorbed through the gastro-intestinal and respiratory tracts and significantly through the skin. Their key action is to inhibit acetylcholinesterase which occurs especially in the nicotinic and muscarinic receptors of nerve, muscle, and brain grey matter. Acetylcholine then accumulates at neuromuscular junctions causing depolarization of skeletal muscle, resulting in weakness and fasciculations. In the central nervous system, neural transmission is disrupted. Reactivation ("recovery") of this enzyme occurs very slowly but can be speeded up by a cholinesterase-reactivating agent such as pralidoxime.

The time of onset of the toxicity and its duration vary enormously depending on the organophosphates implicated. The phosphorothioates are more lipophilic and more chemically stable than the phosphates and must be biotransformed (activated) to become biologically active. This means that the onset of features after exposure may be delayed and intoxication may be prolonged because of storage in fat. In contrast, phosphates are biologically active and therefore after exposure features may appear more quickly.

Recent research has indicated that the presence of solvents in commercial formulations may account for much of their toxicity [4]. By reducing the toxicity to mammals in these agricultural preparations may significantly reduce the deaths from suicidal attempts.

What are their clinical effects?

The patient may have been exposed at the time of agricultural spraying of crops in an enclosed space. Deliberate self-poisoning with an organophosphate is unusual in western countries but common in Africa.

The **acute effects** can appear within hours and depend on the way in which the person has been exposed:

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inhalation, skin, ingestion (swallowing) and eye contact.

Inhalation:

- Chest tightness and wheezing,
- Cough,
- Frothy sputum (bronchorrhoea) and pulmonary oedema,
- Systemic features.

Skin:

- Localized sweating,
- Muscle fasciculation,
- Systemic features.

Ingestion:

- Increased salivation,
- Nausea and vomiting,
- Diarrhoea (often watery),
- Cramping abdominal pains,
- Involuntary defaecation,
- Systemic features.

Eye:

- Constricted pupils (miosis),
- Pain,
- Lacrimation (excess tears),
- Blurred vision.

Systemic features may include:

- Increased sweating,
- Uncontrolled defaecation and urination,
- Anxiety, restlessness and confusion,
- Muscle weakness, cramps and fasciculation,
- Ataxia and tremor,
- Headache and dizziness,
- Epileptics fits,
- Cardiac and respiratory failure,
- Glycosuria and hyperglycaemia.

The **physical signs of acute poisoning** are as would be expected from excess acetylcholine action: pin-point pupils (constricted), marked sweating, muscle fasciculation and (especially proximal) muscle weakness. The neck flexor and eye (extra-ocular) muscles are particularly affected. If the respiratory muscles are involved leading to respiratory failure then prognosis is poor. Bradycardia or tachycardia, cardiac dysrhythmias and marked hypotension may also occur. However there are later consequences of organophosphate poisoning as follows:

- **Intermediate syndrome:** Relapse after apparent resolution of cholinergic symptoms has been reported in patients, particularly in those who have ingested highly lipophilic organophosphate insecticides, and is termed the "intermediate" syndrome. Paralysis of limb muscles, neck flexors and cranial nerves develops some 24-96 hours after exposure and probably represent the nicotinic effects of acetylcholine.
- **Delayed neuropathy:** organophosphate-induced delayed neuropathy can also result rarely from acute exposure to some organophosphate insecticides (e.g. chlorpyrifos, dichlorvos, isofenphos, metamidophos, trichlorfon). This delayed neuropathy is initiated by phosphorylation and subsequent aging of at least 70% of neuropathy target esterase in peripheral nerves and occurs within hours of poisoning. The features are characterised by distal degeneration of some axons of both the peripheral and central nervous systems occurring 1-4 weeks after single or short-term exposures. Cramping muscle pain in the lower limbs, distal numbness and paraesthesiae occur, followed by progressive weakness, depression of deep tendon reflexes in the lower limbs and, in severe cases, in the upper limbs. Signs include high-stepping gait associated with bilateral foot drop and, in severe cases, quadriplegia with foot and wrist drop as well as pyramidal signs. In time, there might be significant recovery of the peripheral nerve function but, depending on the degree of pyramidal involvement, spastic ataxia may be a permanent outcome.

Diagnosis

This is usually obvious from the history (often obtained from attendants), symptoms and physical signs. It can be confirmed by measuring plasma or red blood cell acetylcholinesterase levels but such tests are highly unlikely to be available. Even if they were available treatment must not await the results.

The differential diagnosis of the long-term neurological features must include:

- Guillain-Barré syndrome (acute inflammatory polyneuropathy),
- Diabetic neuropathies,
- HIV-related neuropathies,
- Myasthenia gravis,
- Neuropathies caused by other toxic chemicals.

Management

It is essential to protect of all members of the medical team from contact with any organophosphate on the patient's clothing and from vomitus. Surgical gloves should be worn. After starting the stabilization and treatment the patient should be decontaminated by removing and

carefully disposing of all clothing and then washing the patient with soap and water.

As with all patients at mortal risk resuscitation and stabilisation are priorities and the **"ABC"** should always be remembered: **A**irway, **B**reathing (ventilation) and **C**irculation. A note of the Glasgow Coma Score is a useful baseline from which to monitor subsequent progress.

Oxygen should be given and intravenous (IV) access established. IV fluids should be administered according to observations with special attention to the risk of the development of pulmonary oedema. If the latter occurs then the careful use of IV furosamide may help.

There is little evidence that gastric lavage will improve outcomes. Indeed it may even worsen the outcome especially if the airway is not adequately protected. If the procedure is used it should only be carried out if the toxic agent has been taken up to an hour before [5,6].

In the past activated charcoal has been given by mouth in an attempt to reduce absorption of a toxic agent [7,8]. There appears to be little evidence of benefit in organophosphate poisoning. It can be messy to administer and if the patient is vomiting and perhaps has respiratory depression then there are added dangers to the airway.

In adults the routine use of diazepam 5 – 10mg IV reduces anxiety and suppresses fits. It is important to note that phenothiazines (e.g chlorpromazine) **should not** be used for sedation as they have an anticholinesterase effect and so would make the situation worse. **A careful watch of respiratory function is essential when any form of sedation is given.**

Atropine will block the muscurinic effects of acetylcholine. For an adult the dose is 1 – 3 mg IV and then repeated by doubling the dose every five minutes until there are signs of a beneficial response. This is noted by the clearance of bronchorrhoea and bronchospasm and the pulse rising above 80 / minute and systolic blood pressure above 80mmHg. Subsequent administration should be sufficient to maintain stability as noted by these observations. Some patients are resistant to the effects of atropine and need large doses possibly up to 100mg in 24 hours. Too much atropine (atropine intoxication) is indicated by a tachycardia, dry mouth and skin and an abdominal ileus. **For a child** the initial dose of atropine is 0.02 mg / kg. Atropinisation should be maintained for 48 hours.

The use of an **oxime** (e.g. **pralidoxime chloride**) has been suggested as beneficial if the patient is treated at an early stage after taking the organophosphate. They work by reactivating cholinesterase. The loading dose is 30 mg / kg given by IV injection **over 30 minutes.** If benefit follows, as reflected by improved muscle power and less fasciculation and convulsions and improved conscious level, then an infusion should be provided at 8 – 10 mg/kg/hour and maintained until atropine has not been needed for up to 24 hours. **The use of an oxime should never replace the administration of atropine.** In my experience a supply of an oxime has not been available where I have worked. **However** a recent review [9] of the literature does not support this "standard" recommendation as beneficial, although it is possible that certain subgroups of patients might benefit. Further research is needed to establish the best doses and for whom.

It is essential that all patients poisoned with an organophosphate are constantly and regularly monitored by the nursing and medical staff:

1. Hourly pulse, blood pressure and respiratory rate charts.
2. Fluid balance charts.
3. Glasgow Coma Scale chart.
4. A baseline electrocardiogram recording could prove valuable later as may an initial assessment of blood urea, creatinine and electrolytes although it is appreciated that facilities are often not available.
5. Any deterioration in respiratory function should be taken as an indication for possible artificial ventilation.

Post-recovery management

When a patient recovers from a self-poisoning event it is not the end of the medical team's responsibility. An assessment of the patient's psychosocial state is necessary to indicate an underlying psychiatric disorder and the risk of repetition [10]. A sympathetic and non-judgmental approach must always be adopted.

Practice points

- Self-poisoning with organophosphates is common in developing countries with a high mortality.
- Rapid initial assessment, resuscitation, stabilisation and administration of atropine is crucial.
- The value of oximes remains uncertain.
- Close and careful monitoring of the patient will alert the medical team to life-saving intervention.
- The mortality can be reduced.
- Post-recovery assessment and care are essential.

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Acknowledgment

The author is most grateful to Professor Allister Vale (Director, National Poisons Information Service (Birmingham Unit) and West Midlands Poisons Unit, City Hospital, Birmingham, UK.) for his valuable comments during the writing of this review.