Management of acute organophosphorus pesticide poisoning

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Organophosphorus pesticide self-poisoning is an important clinical problem in rural regions of the developing world, and kills an estimated 200 000 people every year. Unintentional poisoning kills far fewer people but is a problem in places where highly toxic organophosphorus pesticides are available. Medical management is difficult, with case fatality generally more than 15%. We describe the limited evidence that can guide therapy and the factors that should be considered when designing further clinical studies. 50 years after first use, we still do not know how the core treatments—atropine, oximes, and diazepam—should best be given. Important constraints in the collection of useful data have included the late recognition of great variability in activity and action of the individual pesticides, and the care needed cholinesterase assays for results to be comparable between studies. However, consensus suggests that early resuscitation with atropine, oxygen, respiratory support, and fluids is needed to improve oxygen delivery to tissues. The role of oximes is not completely clear; they might benefit only patients poisoned by specific pesticides or patients with moderate poisoning. Small studies suggest benefit from new treatments such as magnesium sulphate, but much larger trials are needed. Gastric lavage could have a role but should only be undertaken once the patient is stable. Randomised controlled trials are underway in rural Asia to assess the effectiveness of these therapies. However, some organophosphorus pesticides might prove very difficult to treat with current therapies, such that bans on particular pesticides could be the only method to substantially reduce the case fatality after poisoning. Improved medical management of organophosphorus poisoning should result in a reduction in worldwide deaths from suicide.

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Organophosphorus pesticide self-poisoning is a major clinical and public-health problem across much of rural Asia.[1–3] Of the estimated 500 000 deaths from self-harm in the region each year,[4] about 60% are due to pesticide poisoning.[3] Many studies estimate that organophosphorus pesticides are responsible for around two-thirds of these deaths[5]—a total of 200 000 a year.[3] Deaths from unintentional organophosphorus poisoning are less common than those from intentional poisoning[6] and seem to be more common in regions where highly toxic organophosphorus pesticides (WHO Class I toxicity) are available.[7,8] In a large cohort of Sri Lankan patients poisoned with WHO Class II organophosphorus pesticides,[9,10] no deaths resulted from unintentional poisoning (Eddleston M, unpublished).

Hospitals in rural areas bear the brunt of this problem, seeing many hundreds of patients poisoned by pesticides each year, with a case fatality of 15–30%.[5,11] Unfortunately, these hospitals are frequently not adequately staffed or equipped to deal with these very sick patients—intensive care beds and ventilators are in short supply—so even unconscious patients are managed on open wards (figure 1). Furthermore, the evidence for treatment is weak[12] and if evidence of benefit does exist for particular antidotes, they are poorly used[13–15] or unavailable.[3]

Improved medical management and provision of antidotes and intensive care beds, together with bans on the most toxic pesticides,[16] should reduce the case fatality for self-poisoning and noticeably reduce the number of deaths from self-harm in rural Asia.[3,12]

Search strategy and selection criteria

We searched for relevant studies by searching PubMed (1960–2006), Embase (1974–2006), UK National Research Register, Cochrane Injuries Group Specialised Register, Clinicaltrials.gov and the Cochrane databases (all until Dec 2006) for "organophosphorus", "organophosphate", or "organic phosphorus" and "poisoning" or "toxicity". We did not limit the search by language; however, we had limited ability to translate papers from China where many studies have been done. Translation of Chinese papers was therefore ordered according to relevance, established by review of English abstracts. We also used information from our continuing studies in Sri Lanka that have recruited more than 2000 patients poisoned with organophosphate, and from discussions with clinicians seeing such patients across Asia.

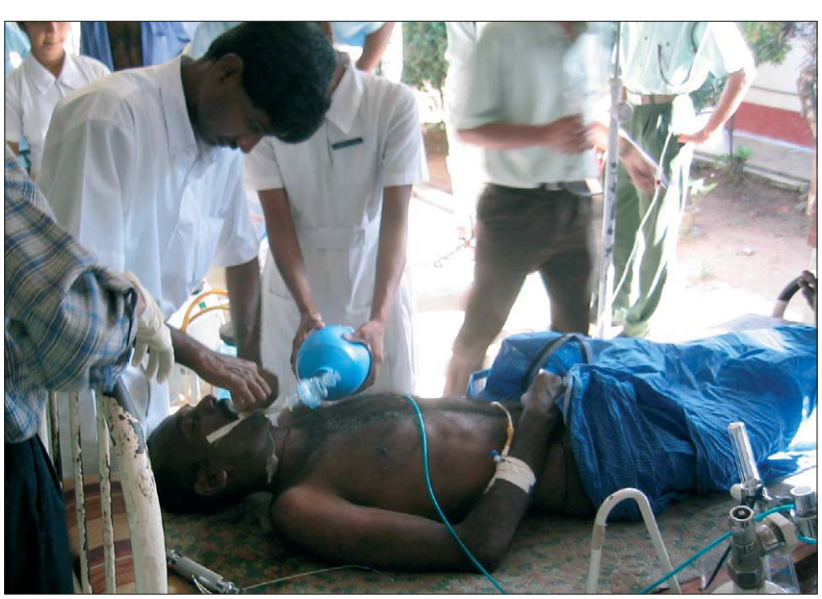

Figure 1: **Management of a patient with severe organophosphorus poisoning in a Sri Lankan district hospital**
The absence of intensive-care beds and ventilators means that unconscious patients are frequently intubated and ventilated on the open ward. This figure is reproduced with permission from the corresponding author.

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Pathophysiology

Organophosphorus pesticides inhibit esterase enzymes, especially acetylcholinesterase (EC 3.1.1.7) in synapses and on red-cell membranes, and butyrylcholinesterase (EC 3.1.1.8) in plasma.[17] Although acute butyrylcholinesterase inhibition does not seem to cause clinical features, acetylcholinesterase inhibition results in accumulation of acetylcholine and overstimulation of acetylcholine receptors in synapses of the autonomic nervous system, CNS, and neuromuscular junctions.[17] The subsequent autonomic, CNS, and neuromuscular features of organophosphorus poisoning are well known (panel 1).

Patients can suddenly develop peripheral respiratory failure while conscious after seemingly recovering from cholinergic crisis, which is termed type II respiratory failure or intermediate syndrome.[21,22] This syndrome is an important cause of death in patients who have been resuscitated and stabilised on admission to hospital.

Diagnosis is made on the basis of clinical suspicion, the characteristic clinical signs, smell of pesticides or solvents, and reduced butyrylcholinesterase or acetylcholinesterase activity in the blood.[17] Patients with severe organophosphorus poisoning typically present with pinpoint pupils, excessive sweating, reduced consciousness, and poor respiration. The major differential diagnosis is carbamate poisoning, which is clinically indistinguishable.[18]

Panel 1: Clinical features of organophosphorus pesticide poisoning[18–20]

Features due to overstimulation of muscarinic acetylcholine receptors in the parasympathetic system
- Bronchospasm
- Bronchorrhoea
- Miosis
- Lachrymation
- Urination
- Diarrhoea
- Hypotension
- Bradycardia
- Vomiting
- Salivation

Features due to overstimulation of nicotinic acetylcholine receptors in the sympathetic system
- Tachycardia
- Mydriasis
- Hypertension
- Sweating

Features due to overstimulation of nicotinic and muscarinic acetylcholine receptors in the CNS
- Confusion
- Agitation
- Coma
- Respiratory failure

Features due to overstimulation of nicotinic acetylcholine receptors at the neuromuscular junction
- Muscle weakness
- Paralysis
- Fasciculations

Patients usually present with features of parasympathetic overstimulation. A few might show signs of sympathetic stimulation, including tachycardia. However, tachycardia can also be caused by hypovolaemia, hypoxia, previous doses of atropine, and alcohol withdrawal. Respiratory failure can be due to bronchospasm, bronchorrhoea (both reversible with atropine), and dysfunction of neuromuscular junctions and the CNS.

Cholinesterase assays

Diagnosis of organophosphorus poisoning should ideally be confirmed with an assay to measure butyrylcholinesterase activity in plasma (or acetylcholinesterase in whole blood).[17] However, the results of such assays are rarely available in time to affect clinical decisionmaking. Their importance is for guidance of clinical research; understanding of their limitations is essential for

Panel 2: Drawbacks of cholinesterase activity assays[23]

Plasma butyrylcholinesterase assays
- Inhibition of butyrylcholinesterase, also called plasma cholinesterase or pseudocholinesterase, does not give information about clinical severity of the poisoning. Many organophosphorus pesticides are more potent inhibitors of butyrylcholinesterase than they are of acetylcholinesterase; butyrylcholinesterase inhibition might occur to a greater extent than acetylcholinesterase inhibition.[9] Butyrylcholinesterase assays can be used to detect exposure to an organophosphorus or carbamate pesticide
- Butyrylcholinesterase is produced by the liver, and blood concentrations recover by about 7% of normal each day once the organophosphorus has been eliminated.[24] Daily butyrylcholinesterase assays can be used to monitor when enzyme activity starts to rise again, since this recovery suggests that the organophosphorus has been eliminated (figure 2)
- Variation between commercial assays can make comparisons between studies difficult. The concentration of butyrylthiocholine varies between assays. A high concentration substrate (eg, 7 mM *vs* 1 mM) will result in a 30% higher measured activity and a higher background[25]
- Measurement of butyrylthiocholine hydrolysis in the absence of plasma is needed to measure non-enzymatic hydrolysis and hence background values. Not all commercial assays provide such a control. The background amount of spontaneous butyrylthiocholine hydrolysis is affected by its concentration and pH, which both vary between assay kits[25]
- Temperature control is important, because butyrylcholinesterase activity increases by some 4% per 1°C increase in temperature[26]

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Red cell acetylcholinesterase assays

- These assays measure acetylcholinesterase expressed on the surface of red cells. Red-cell acetylcholinesterase inhibition is a good marker of such inhibition in synapses and of poisoning severity. This enzyme is measured in whole blood in which butyrylcholinesterase activity has been blocked by an inhibitor. Acetylcholinesterase is present at very low levels in human plasma and serum[27]
- Once red-cell acetylcholinesterase has aged, it only recovers via erythropoeisis. Regeneration at less than 1% per day is therefore much slower than butyrylcholinesterase regeneration. The rate of spontaneous neuronal acetylcholinesterase recovery is unclear, and thus red-cell acetylcholinesterase could be a less useful marker of synaptic acetylcholinesterase activity as recovery occurs
- Reactions between acetylcholinesterase, organophosphorus and oximes will continue if a blood sample is left at room temperature after sampling. The measured acetylcholinesterase activity will then not represent the exact activity in the blood at the time of sampling; leaving samples for different times will give variation in assays. Blood samples must be diluted and cooled immediately after sampling, to stop the reactions. We routinely dilute by a factor of 20 at the bedside by mixing 200 µL of blood freshly drawn into an EDTA tube with 4 mL of cold saline (at 4˚C) and then place the sample in a freezer at −20˚C within 5 min
- Incubation of an aliquot of blood with a large quantity of oxime (eg, 100 µmol/L obidoxime) for 15 min before assay will reactivate any acetylcholinesterase that has not aged. Such an assay could potentially be used to establish whether a patient might benefit from continued oxime therapy or from higher doses
- Acetylcholinesterase assays are sensitive to the concentration of oxime and substrate, and pH. Assays with a low substrate concentration, pH 7·4, and therapeutic oxime concentrations will reduce background signal in the assay;[23,28] however, a blank sample without plasma is needed to quantify the background signal
- Matrix sulfhydryl compounds in red cells (mainly haemoglobin) react with Ellman's reagent. This reaction should be completed by preincubation of red-cell samples with the reagent during temperature equilibration. A higher background activity will be recorded if this procedure is not done

Monitoring a patient's cholinesterase status after organophosphate poisoning enables the verification of substantial exposure to anticholinesterase agents. In future, such assays could facilitate the decision about when to stop oxime treatment and allow cautious weaning of a patient from a ventilator when butyrylcholinesterase activity is increasing. Studies are underway to confirm the clinical usefulness of this approach.

interpretation of studies looking at individual pesticides and specific interventions.

Unfortunately, much confusion exists about the use and interpretation of these assays (panel 2). Some pesticides inhibit butyrylcholinesterase more effectively than they inhibit acetylcholinesterase.[9] Butyrylcholinesterase activity does not relate to severity of poisoning; however, it can be used as a sensitive marker of exposure to most organophosphorus compounds or other cholinesterase-inhibiting compounds, and for measuring organophosphorus elimination from the body (figure 2).

Studies suggest that red-cell acetylcholinesterase is a good marker of synaptic function and atropine needs in patients poisoned with organophosphorus, and is therefore probably a good marker of severity.[29,30] Patients with red-cell acetylcholinesterase activity of at least 30% had normal muscle function and no need for atropine. By contrast, patients with less than 10% of normal red-cell acetylcholinesterase activity had grossly deranged muscle function and needed high doses of atropine. Acetylcholinesterase activity between these values was associated with moderate impairment of muscle function and need for atropine.

A major drawback of acetylcholinesterase assays is that the interaction between organophosphorus, acetyl-

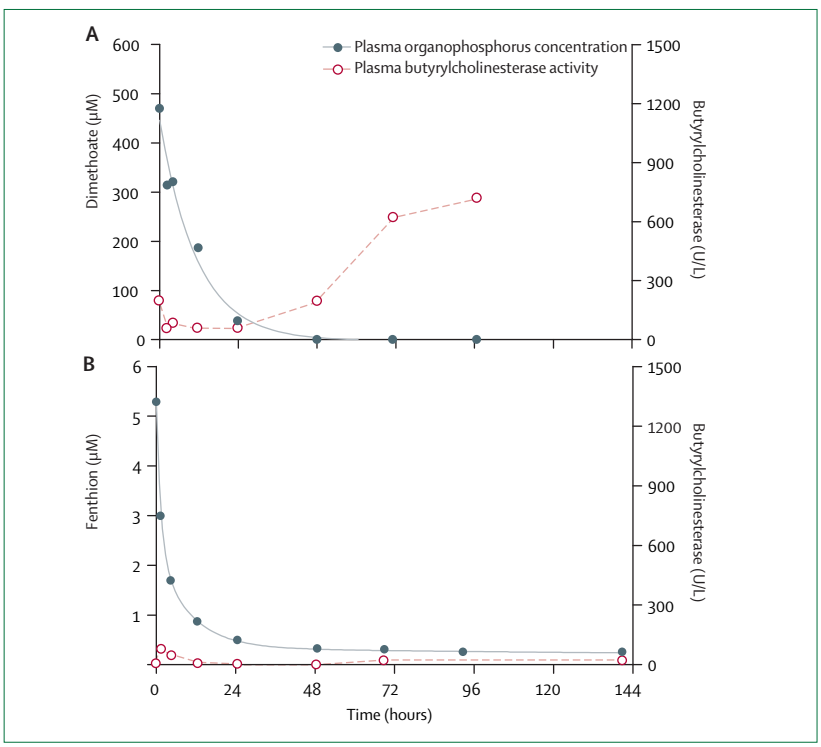

Figure 2: **Use of butyrylcholinesterase recovery as a marker of organophosphorus pesticide elimination in (A) dimethoate and (B) fenthion poisoning**

Dimethoate is hydrophilic and rapidly excreted from the body. Plasma butyrylcholinesterase activity therefore begins to rise again within two days of ingestion. By contrast, fenthion is fat soluble and slowly redistributes into the blood after initial distribution into the fat. As a result, fenthion is detectable in the blood for many days and butyrylcholinesterase activity remains inhibited.

***Panel 3:* Summary of treatment**[20,31,32]

- Check airway, breathing, and circulation. Place patient in the left lateral position, preferably with head lower than the feet, to reduce risk of aspiration of stomach contents. Provide high flow oxygen, if available. Intubate the patient if their airway or breathing is compromised
- Obtain intravenous access and give 1–3 mg of atropine as a bolus, depending on severity. Set up an infusion of 0·9% normal saline; aim to keep the systolic blood pressure above 80 mm Hg and urine output above 0·5 mL/kg/h
- Record pulse rate, blood pressure, pupil size, presence of sweat, and auscultatory findings at time of first atropine dose
- Give pralidoxime chloride 2 g (or obidoxime 250 mg) intravenously over 20–30 min into a second cannula; follow with an infusion of pralidoxime 0·5–1 g/h (or obidoxime 30 mg/hr) in 0·9% normal saline
- 5 min after giving atropine, check pulse, blood pressure, pupil size, sweat, and chest sounds. If no improvement has taken place, give double the original dose of atropine
- Continue to review every 5 min; give doubling doses of atropine if response is still absent. Once parameters have begun to improve, cease dose doubling. Similar or smaller doses can be used
- Give atropine boluses until the heart rate is more than 80 beats per minute, the systolic blood pressure is more than 80 mm Hg, and the chest is clear (appreciating that atropine will not clear focal areas of aspiration). Sweating stops in most cases. A tachycardia is not a contraindication to atropine since it can be caused by many factors (panel 1). The pupils will commonly dilate; however, this sign is not a useful endpoint for initial atropine treatment because a delay exists before maximum effect. However, very dilated pupils are an indicator of atropine toxicity
- Clinical judgment is needed about additional doses of atropine if the heart rate and blood pressure are slightly below their targets but the chest is clear. More atropine at this point might not be needed. Severe hypotension might benefit from vasopressors. The value of vasopressors versus higher doses of atropine is not yet clear[33,34]
- Once the patient is stable, start an infusion of atropine giving every hour about 10–20% of the total dose needed to stabilise the patient. Check the patient often to see if too much or too little atropine is being given. If too little is given, cholinergic features will re-emerge after some time.[31] If too much is given, patients will become agitated and pyrexial, and develop absent bowel sounds and urinary retention. If this happens, stop the infusion and wait 30–60 min for these features to settle before starting again at a lower infusion rate
- Continue the oxime infusion until atropine has not been needed for 12–24 h and the patient has been extubated
- Continue to review respiratory function. Intubate and ventilate patients if tidal volume is below 5 mL/kg or vital capacity is below 15 mL/kg, or if they have apnoeic spells, or PaO_2 is less than 8 kPa (60 mm Hg) on F_IO_2 of more than 60%
- Assess flexor neck strength regularly in conscious patients by asking them to lift their head off the bed and hold it in that position while pressure is applied to their forehead. Any sign of weakness is a sign that the patient is at risk of developing peripheral respiratory failure (intermediate syndrome). Tidal volume should be checked every 4 h in such patients. Values less than 5 mL/kg suggest a need for intubation and ventilation
- Treat agitation by reviewing the dose of atropine being given and provide adequate sedation with benzodiazepines. Physical restraint of agitated patients in warm conditions risks severe hyperthermia, which is exacerbated greatly by atropine because it inhibits normal thermoregulatory responses, including sweating. Adequate sedation is therefore important
- Monitor frequently for recurring cholinergic crises due to release of fat soluble organophosphorus from fat stores. Such crises can occur for several days to weeks after ingestion of some organophosphorus. Patients with recurring cholinergic features will need retreatment with atropine and oxime

cholinesterase, and oximes continues if the sample is left at room temperature for even a few minutes (panel 2). To obtain reliable results, the reaction must be stopped immediately by cooling and dilution of the sample as soon as it is taken from the patient. Otherwise differences of only a few minutes in the time taken to cool a sample will cause notable variation over repeated samples, which makes interpretation difficult.

Principles of therapy

Treatment includes resuscitation of patients and giving oxygen, a muscarinic antagonist (usually atropine), fluids, and an acetylcholinesterase reactivator (an oxime that reactivates acetylcholinesterase by removal of the phosphate group) (panel 3).[35] Respiratory support is given as necessary. Gastric decontamination should be considered only after the patient has been fully resuscitated and stabilised. Patients must be carefully observed after stabilisation for changes in atropine needs, worsening respiratory function because of intermediate syndrome, and recurrent cholinergic features occuring with fat-soluble organophosphorus.

Few randomised trials of such poisoning have been done; consequently the evidence base is restricted.[35] Both atropine and oximes were introduced into clinical practice rapidly in the 1950s without clinical trials.[36,37] As a result, we do not know the ideal regimens for either therapy. Trials of other interventions are hindered because the best way to give the core treatments has not yet been determined and is highly variable in practice. This variability interferes with development of a widely accepted study protocol and limits the external validity of study results.

Efficacy of treatment and outcome

The case fatality reported by hospitals varies markedly—from 1·85% in the Posion Control Centre of Mach Mai hospital, Hanoi, Vietnam to 40% in a German intensive-care unit (Pham Due, Personal Communication).[38,39] Since so few randomised trials have been done, comparison of effectiveness of therapies given in different hospitals is tempting. Unfortunately, such comparisons are confounded by many factors (panel 4).

In particular, although many textbooks regard poisoning with various organophosphorus pesticides to be broadly similar and equally responsive to treatment, differences in chemistry have major consequences for treatment efficacy.[9,48] The pesticide ingested defines how many patients survive to reach medical attention, how ill they are at admission, effectiveness of oxime therapy, likelihood of recurrent cholinergic crises, or need for respiratory support (panel 4). Such variation reaffirms the importance of randomised trials to measure effectiveness of treatments for specific pesticides.

Initial stabilisation

Severe acute organophosphorus pesticide poisoning is a medical emergency. Treatment must ensure that the

patient has a patent airway and adequate breathing and circulation. Ideally, oxygen should be provided at the first opportunity. However, little evidence supports the common advice that atropine must not be given until oxygen is available.[17,19,49,50] In hospitals that have no access to oxygen, atropine should be given early to patients with pesticide poisoning to reduce secretions and improve respiratory function.[32] The patient should be placed in the left lateral position, with the neck extended. This position reduces risk of aspiration, helps keep the airway patent, and could decrease pyloric emptying and absorption of poison.[51,52] Supportive care should include giving fluids and control of blood glucose.

Health-care workers are thought to be at risk of poisoning during initial stabilisation of patients poisoned with organophosphorus.[53,54] A few Western hospitals have reported cases of such poisoning, but none have shown inhibition of acetylcholinesterase or butyrylcholinesterase in health-care workers consistent with substantial exposure to organophosphorus.[55] Some symptoms, such as headaches and nausea, are possibly due to anxiety or exposure to the organic solvent (eg, xylene) in which the pesticide is mixed.[55,56]

Hundreds of thousands of patients with severe organophosphorus poisoning are seen every year in basic hospitals across Asia; health-care workers take no special precautions and no cases of secondary poisoning have been reported. Reticence by hospital workers to treat patients poisoned with pesticides puts patients at risk. Guidelines recommend universal precautions, maximum ventilation, and frequent rotation of staff, so that effects of solvent and pesticide are kept to a minimum.[55]

Muscarinic antagonist drugs

Although atropine remains the mainstay of therapy worldwide,[14,49] other muscarinic antagonists have been studied in animals.[49] An important difference between such drugs is their penetration into the CNS.[57] Glycopyrronium bromide and hyoscine methobromide do not enter the CNS, but hyoscine has excellent penetration; atropine enters the CNS, but not to the same degree as hyoscine.

The main adverse-effect of atropine is anticholinergic delirium in patients who receive too high a dose.[49] Some physicians therefore prefer glycopyrronium to treat the peripheral effects of organophosphorus without causing confusion. However, its poor CNS penetration suggests that it is ineffective at countering coma and reduced respiration seen in patients with the cholinergic syndrome. A small randomised controlled trial comparing glycopyrronium with atropine noted no significant difference in mortality or ventilation rates, but it did not have sufficient power to detect small differences between treatments.[58]

Hyoscine was used successfully to treat a patient with severe extra-pyramidal features but few peripheral signs.[59] Animal studies suggest that it is more effective than

***Panel 4:* Factors affecting outcome in organophosphorus pesticide self-poisoning**

- Toxicity: toxicity is usually rated according to the oral LD50 in rats. This scale is able to roughly differentiate between very safe and very toxic pesticides—for example parathion (LD50 13 mg/kg,[40] WHO: Class IA) is highly toxic while temephos (LD50 8600 mg/kg,[40] WHO: unlikely to cause acute hazard) has not been associated with deaths. However, large differences in human toxicity have been seen after poisoning with organophosphates with roughly the same animal toxicity,[9,11] and this classification does not account for the effects of treatment[9]
- Impurities: the WHO toxicity classification assesses fresh pesticide from approved manufacturers. Pesticide storage in hot conditions can result in chemical reactions that have toxic products. Such a process was blamed for the death of pesticide sprayers using malathion in Pakistan in the late 1970s[41,42] and has also been noted with both diazinon and dimethoate[43,44]
- Formulation: a pesticide's toxicity will vary according to formulation, which differs according to the organophosphorus and the place of manufacture. For example, malathion is available as an 80% solution in street-side pesticide stalls in Burma, but as a 3% powder in Sri Lanka
- Alkyl sub-groups: most pesticides have either two methyl groups attached via oxygen atoms to the phosphate (dimethyl organophosphorus) or two ethyl groups (diethyl organophosphates) (figure 3). Acetylcholinesterase ageing is much faster for dimethyl poisoning than for diethyl poisoning, therefore to be effective, oximes must be given quickly to patients with dimethyl poisoning (panel 5). A few pesticides have atypical structures, with another alkyl group (eg, propyl in profenofos) attached to the phosphate group via a sulphur atom. These organophosphorus pesticides age acetylcholinesterase even faster and oximes are probably not effective
- Need for activation. Many compounds are inactive thioates (with a double-bonded sulphur attached to the phosphorus atom) and have to be desulphurated to make the active oxon, via cytochrome P450 enzymes in the gut wall and liver. The P450 3A4 seems to be the most active enzyme when organophorus is present in high concentrations, as happens after self-poisoning[45]
- Speed of activation and of AChE inhibition. The rate of activation of thioate organophosphates varies between pesticides.[45,46] Large variation also exists in the rate of acetylcholinesterase inhibition between organophosphorus pesticide oxons[13]
- Duration of effect—fat solubility and half-life. Some fat soluble thioate organophosphorus pesticides (eg, fenthion) distribute in large amounts to fat stores after absorption. This seems to reduce the peak blood organophosphorus concentration and the early cholinergic features are usually mild. Subsequent slow redistribution and activation causes recurrent cholinergic features lasting days or weeks. Peripheral respiratory failure is common with these organophosphorus, probably due to continuing inhibition of acetylcholinesterase. Ageing only starts after acetylcholinesterase inhibition, so oximes could theoretically be beneficial for many days in such patients. By contrast, other organophosphorus (eg, dichlorvos) do not need activation, are not fat soluble, and could have a much more rapid onset of effect and shorter duration of activity. Fat solubility is graded according to the Kow (logarithm octanol/water coefficient): less than 1·0=not fat soluble; more than 4·0=very fat soluble[47]

The above factors have important consequences for the speed of onset of organophosphorus poisoning after ingestion. Ingestion of an oxon organophosphorus that rapidly inhibits acetylcholinesterase will result in early onset of clinical features and respiratory arrest before presentation to hospital, increasing the risk of hypoxic brain damage and aspiration. The conversion of the thioate organophosphorus parathion to paraoxon is so fast that patients can be unconscious in 20 min. Clinical features after poisoning by other thioate organophosphorus, such as dimethoate and fenthion, happen later, giving the patient more time to present to hospital.

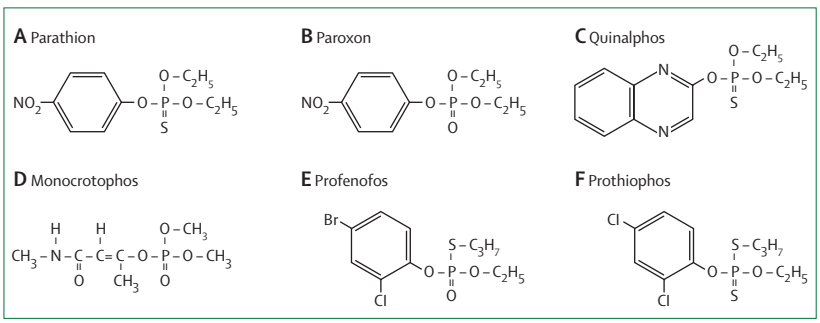

Figure 3: **Chemical classes of organophosphorus pesticides**
Structures of organophosphorus pesticides from diethyl (A, B, C), dimethyl (D), and S-alkyl (E,F) classes. Most organophosphorus pesticides are thioates, with a double-bonded sulphur atom linked to the phosphate (A, C, F) that needs to be converted to the active oxon (eg, A to B). A few organophosphorus pesticides are oxons (eg, D, E) and do not need activation; they are able to inhibit acetylcholinesterase directly as soon as they are absorbed.

atropine for control of seizures induced by inhaled organophosphorus nerve agents.[60] However, extrapyramidal effects and seizures are not common features of organophosphorus poisoning.[9,21]

Atropine will probably remain the antimuscarinic agent of choice until high-quality randomised trials show another muscarinic antagonist to have a better benefit-to-harm ratio because it is available widely, affordable, and moderately able to penetrate into the CNS. No known randomised controlled trials have compared different regimens of atropine for either loading or continuation therapy. As a result, many different recommendations have been made—a 2004 review noted more than 30 dosing regimens, some of which would take many hours to give the full loading dose of atropine.[15]

The aim of early therapy is to reverse cholinergic features and to improve cardiac and respiratory function as quickly as possible. We use a regimen of doubling doses[18] (panel 2), with the aim of raising the pulse above 80 beats per minute and systolic blood pressure above 80 mm Hg, and rapidly reversing bronchospasm and bronchorrhoea. This regimen allows for as much as 70 mg of atropine to be given in stages to a patient in less than 30 min, resulting in rapid stabilisation and low risk of atropine toxicity.[15] A study from south India[61] recorded benefit from an infusion of atropine compared with repeated bolus doses, but it used historical controls thus reducing confidence in this finding. Infusions could reduce fluctuations in blood atropine concentration, reducing the need for frequent patient observation, an important benefit in hospitals with few staff.

Oximes

Oximes reactivate acetylcholinesterase inhibited by oganophosphorus.[13] Pralidoxime was discovered in the mid-1950s by Wilson and colleagues, and was soon successfully introduced into clinical practice for patients with parathion poisoning.[37] Other oximes, such as obidoxime and trimedoxime, have been developed but pralidoxime remains the most widely used. It has four salts: chloride, iodide, metilsulfate, and mesilate.[62] The chloride and iodide salts are used widely, but metilsulfate and mesilate are used mostly in France, Belgium, and the UK. The chloride salt has advantages over iodide—in particular its smaller molecular weight (173 *vs* 264), which provides 1·5-times more active compound per gram of salt than does iodide. High doses of pralidoxime iodide also puts patients at risk of thyroid toxicity, especially if given for a long period.[63]

Despite the beneficial effects of pralidoxime first noted with parathion poisoning, its effectiveness has been much debated, with many Asian clinicians unconvinced of its benefit.[64–66] In particular, two randomised controlled trials in Vellore, India in the early 1990s noted that low-dose infusions of pralidoxime might cause harm.[67,68] The absense of clinical benefit could relate to trial design (suboptimum dose, or bias in allocation). Alternatively, this result could suggest that pralidoxime is ineffective in the patients seen at this hospital, perhaps because of the specific pesticide ingested, the amount ingested, or the patients' long delay before pralidoxime is given.[69,70]

A Cochrane review[71] and two other meta-analyses[72,73] of pralidoxime have been published. The Cochrane review included two randomised controlled trials[68,69] and reported no clear evidence of benefit or harm. The other meta-analyses combined non-randomised or historically controlled observational studies[64,74–78] with randomised controlled trials[67,68,79] reducing confidence[80,81] in their conclusion that oximes are harmful.

Since these meta-analyses were completed, a randomised controlled trial in Baramati, India[82] studied the effect of very-high-dose pralidoxime iodide (2 g loading dose, then 1 g either every hour or every 4 h for 48 h, then 1 g every 4 h until recovery) in 200 patients with moderate organophosphorus poisoning (excluding severely ill patients). The high-dose regimen was associated with reduced case fatality (1% *vs* 8%; odds ratio [OR] 0·12, 95% CI 0·003–0·90), fewer cases of pneumonia (8% *vs* 35%; 0·16, 0·06–0·39), and reduced time on mechanical ventilation (median 5 days *vs* 10 days). Laboratory studies to identify the pesticide ingested and degree of baseline acetylcholinesterase inhibition and subsequent reversal were not done.[63] However, this study suggests that large doses of pralidoxime could have benefit if patients are treated early and have good supportive care.

Observational studies of pralidoxime and obidoxime suggest that the ability to reverse acetylcholinesterase inhibition with oximes varies with the pesticide ingested (figure 4).[9,13,69,83] Acetylcholinesterase inhibited by diethyl pesticides, such as parathion and quinalphos, seems to be effectively reactivated by oximes, but acetylcholinesterase inhibited by dimethyl organophosphorus, such as monocrotophos or oxydemeton-methyl, seems to respond poorly. We noted that acetylcholinesterase inhibited by S-alkyl-linked organophosphorus, such as profenofos, is not reactivated by oximes at all (figure 4). This difference is probably partly because of variation in the speed of

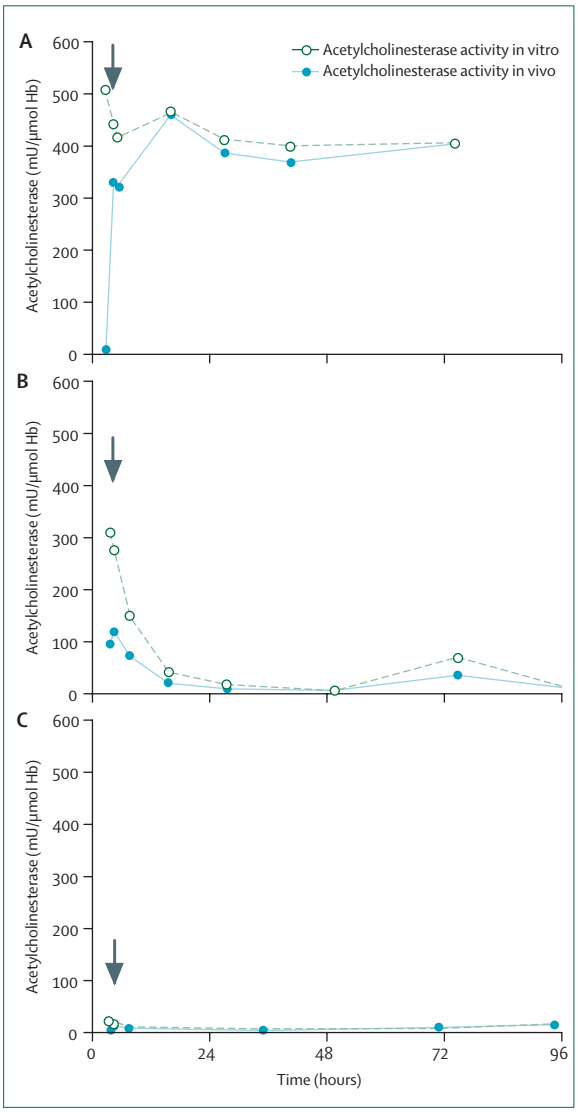

Figure 4: **Variable response to oximes of acetylcholinesterase inhibited by different classes of organophosphorus pesticides**
Acetylcholinesterase was reactivated fully (A) quinalphos, a diethyl pesticide; partially (B) oxydemeton-methyl, a dimethyl pesticide, or not at all (C) profenofos, an S-alkyl pesticide by oximes after poisoning. The arrow shows the time of first dose of pralidoxime. Normal acetylcholinesterase activity is about 600 mU/µmol Hb. In-vitro acetylcholinesterase activity shows how much of the enzyme can be reactivated, i.e. how much of it has not yet aged (in these three cases, on admission when the first dose of pralidoxime was given, A: ~85%, B: ~50%, C: 5%, of the enzyme was not aged). All patients presented to hospital within 4 h.

acetylcholinesterase ageing (panel 5) induced by these different pesticides. Interestingly, the Baramati[82] study did not find a difference in benefit of high-dose pralidoxime in moderate dimethyl or diethyl organophosphorus poisoning. Further studies are needed to establish whether this benefit remains for severe poisoning.

Interpretation of clinical evidence regarding oximes should take into account this variability in response of different pesticides.[69] The clinical effects can also be limited by high concentrations of organophosphorus in the blood after ingestion of a large dose—the pesticide simply re-inhibits any acetylcholinesterase that the oximes reactivate. Oximes will also not be effective for improvement of outcomes if the patient develops severe complications such as aspiration pneumonia or hypoxic brain injury before treatment. Such complications take place most often with fast-acting pesticides such as parathion and dichlorvos.

WHO recommends that oximes be given to all symptomatic patients who need atropine.[14,84] To ensure a therapeutic concentration, a loading dose of pralidoxime chloride or obidoxime is given, then a continuous infusion. The loading dose of oxime should not be given rapidly as a bolus because this method causes vomiting (risking aspiration), tachycardia, and diastolic hypertension.[13]

Panel 5: Reactions of acetylcholinesterase after inhibition with organophosphorus

Inhibited acetylcholinesterase reactivates spontaneously but slowly. The half-life of reactivation varies according to the organophosphorus: if dimethyl, the half-life is about 1 h; if diethyl, the half-life is around 30 h. Oximes speed up this reactivation. Unfortunately, if the organophosphorus is present in high concentrations, newly reactivated acetylcholinesterase will be rapidly reinhibited. Whether reactivation or inhibition predominates depends on the type of organophosphorus and relative concentrations and affinities of organophosphorus and oxime.

Inhibited acetylcholinesterase can also become aged, by loss of one of the two alkyl groups attached to the bound phosphate. Aged acetylcholinesterase cannot be reactivated by oximes. The half-life of ageing varies according to the inhibiting pesticide: if dimethyl, the half-life is around 3 h; if diethyl, the half-life is around 33 h. Thus ageing has important clinical consequences.

If a patient who has ingested a dimethyl pesticide presents to hospital 3 h after ingestion, about 50% of the acetylcholinesterase will already be aged and unresponsive to oximes. A patient arriving after 12 h will have about 94% aged acetylcholinesterase and therefore be unresponsive to oximes. Such a situation is common where patients need to be transferred to a secondary hospital to receive oximes. The situation is better with diethyl pesticides since it takes 33 h for 50% inhibition and oximes can be effective for up to 5 days after ingestion.

Ageing seems to take place much more quickly after poisoning with atypical organophosphorus, such as profenofos, that have neither two methyl groups nor two ethyl groups (figure 3). The half-life of ageing seems to be much less than 1 h, thus oximes are completely ineffective if the patient presents more than an hour or two after ingestion (figure 4).

Benzodiazepines

Patients poisoned with organophosphorus frequently develop agitated delirium. The cause is complex, with contributions from the pesticide itself, atropine toxicity, hypoxia, alcohol ingested with the poison, and medical complications. Although the mainstay of management is prevention or treatment of underlying causes, some patients need pharmacotherapy. Acutely agitated patients will benefit from treatment with diazepam.

Diazepam is first-line therapy for seizures; however, seizures are uncommon in well oxygenated patients with pesticide poisoning.[9,48] Seizures seem to be more common with organophosphorus nerve agents (such as soman and tabun).[85] Animal studies suggest that diazepam reduces neural damage[86] and prevents respiratory failure and death,[87] but studies in humans are few.

Gastrointestinal decontamination

Gastric lavage is often the first intervention poisoned patients receive on presentation to hospital, sometimes at the expense of resuscitation and giving antidote.[88] No evidence shows any form of gastric decontamination to benefit patients poisoned with organophosphorus.[35] Gastric decontamination should only be done after the patient has been stabilised and treated with oxygen, atropine, and an oxime.[88]

Gastric lavage is the most common form of decontamination for organophosphorus poisoning despite the absence of randomised controlled trials to confirm benefit.[35] The rate of absorption of organophosphorus from the human bowel is not known; however, with some pesticides, the rapid onset of poisoning in animals[89] and humans[39] suggests that absorption is rapid, occurring within minutes of ingestion. The time window for effective lavage is therefore probably short. Guidelines for treatment of drug self-poisoning suggest that lavage should be considered only if the patient arrives within 1 hour of ingesting poison.[90] The relevance of these guidelines to organophosphorus poisoning is unclear[91] but lavage should probably only be considered for patients who present soon after ingestion of a substantial amount of toxic pesticide who are intubated, or conscious and willing to cooperate. Repeated gastric lavages are recommended in China to remove pesticide remaining in the stomach,[92] although substantial amounts of organophosphorus are unlikely to remain in the stomach after one lavage.

Ipecacuanha-induced emesis should not be used in organophosphorus pesticide poisoning.[35,93] Patients poisoned with organophosphorus can rapidly become unconscious, risking aspiration if ipecacuanha has been given. Mechanically-induced emesis with large quantities of water risks pushing fluid through the pylorus and into the small bowel, probably increasing the rate of absorption.[93]

A randomised controlled trial of single and multiple doses of superactivated charcoal in Sri Lanka failed to find a significant benefit of either regimen over placebo in more than 1000 patients poisoned with pesticides.[94] Because activated charcoal binds organophosphorus in vitro,[95] the absence of effect in patients might be due to rapid absorption of pesticide into the blood. Alternatively, the ingested dose in fatal cases could be too large for the amount of charcoal given, the charcoal might be given too late, or the solvent might interfere with binding. No evidence suggests that patients with pesticide poisoning benefit from treatment with activated charcoal.

Other therapies

Current therapy works through only a few mechanisms.[96] Several new therapies have been studied but results were inconclusive. However, future research might reveal several affordable therapies working at separate sites that could complement present treatments.

Magnesium sulphate blocks ligand-gated calcium channels, resulting in reduced acetylcholine release from pre-synaptic terminals, thus improving function at neuromuscular junctions, and reduced CNS over-stimulation mediated via NMDA receptor activation.[97] A trial in people poisoned with organophosphorus pesticides recorded reduced mortality with magnesium sulphate (0/11 [0%] *vs* 5/34 [14·7%]; p<0·01).[98] However, the study was small, allocation was not randomised (every fourth patient received the intervention), and the publication incompletely described the dose of magnesium sulphate used and other aspects of the methodology; therefore these results should be interpreted with caution.

The alpha2-adrenergic receptor agonist clonidine also reduces acetylcholine synthesis and release from presynaptic terminals. Animal studies show benefit of clonidine treatment, especially in combination with atropine, but effects in human beings are unknown.[99]

Sodium bicarbonate is sometimes used for treatment of organophosphorus poisoning in Brazil and Iran, in place of oximes.[100,101] Increases in blood pH (up to 7·45–7·55) have been reported to improve outcome in dogs through an unknown mechanism;[102] however, a Cochrane review[103] concluded that insufficient evidence exists at present to establish whether sodium bicarbonate should be used in humans poisoned with organophosphorus.

Removing organophosphorus from the blood could allow optimum action of other therapies. The roles of haemodialysis and haemofiltration are not yet clear; however, a recent non-randomised controlled study in China[104] suggested a benefit of haemofiltration after poisoning with dichlorvos, which has poor solubility in fat, and therefore should have a relatively small volume of distribution. A systematic review of these therapies in organophosphorus poisoning is underway, but randomised controlled trials will be needed to establish good evidence-based treatment guidelines.

Butyrylcholinesterase scavenges organophosphorus in plasma, reducing the amount available to inhibit acetylcholinesterase in synapses.[105] It has been cloned and military research now aims to inject soldiers with the

enzyme before exposure to organophosphorus nerve gases.[106] Such a prophylactic approach is not practical for self-poisoning with organophosphorus because we cannot predict when a person is going to ingest the pesticide. Turkish doctors[107] have reported the use of butyrylcholinesterase in fresh frozen plasma to treat poisoned patients. A small controlled study (12 patients given fresh frozen plasma with 21 control patients) recorded benefit, but this trial was not randomised and allocation decisions were unclear.

Furthermore, whether or not scavenging of organophosphorus by butyrylcholinesterase is the mechanism for any effect of fresh frozen plasma is unclear.[108] In fact, butylcholinesterase seems unlikely to ever be an effective treatment for pesticide poisoning since it binds stoichiometrically to organophosphorus and will be overpowered by the amount of pesticide commonly ingested. For example, 50 mL of 40% dimethoate (molecular weight 229) contains 20 g or 87·3 mmol of organophosphorous, which, if completely absorbed and transformed into the oxon, would need an equivalent number of moles of butyrylcholinesterase (molecular weight about 70 kD; therefore 6 kg) for inactivation.

A better approach than use of butylcholinesterase might be to give recombinant bacterial phosphotriesterases, or hydrolases.[109,110] These proteins break down organophosphorus pesticides enzymatically and protect animals from pesticide poisoning. Future clinical development of such enzymes could reduce blood concentrations of organophosphorus, allowing optimum activity of other treatments.

Conclusion

Medical management of organophosphorus pesticide poisoning is difficult, especially in resource poor locations where most of these patients present. Clinical practice is frequently less than ideal, with poor initial resuscitation and stabilisation, and poor use of antidotes. However, most of the original research regarding acute organophosphorus poisoning in humans has been published in the past decade, which is a positive development. We expect that in the next decade evidence from continuing research by a number of groups across Asia will finally provide clear guidance on how to treat poisoning with organophosphorus pesticides. Hopefully, this new guidance will include the use of novel antidotes that will reduce the case fatality from pesticide poisoning, and therefore reduce the worldwide number of deaths from self-harm.

Contributors

ME wrote the first draft of this manuscript after detailed discussion with the other authors. All authors contributed to draft revisions and approved the final version.

Conflict of interest statement

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