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Pharmacological treatment of organophosphorus insecticide poisoning: the old and the (possible) new

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Despite being a major clinical and public health problem across the developing world, responsible for at least 5 million deaths over the last three decades, the clinical care of patients with organophosphorus (OP) insecticide poisoning has little improved over the last six decades. We are still using the same two antidotes – atropine and oximes – that first came into clinical use in the late 1950s. Clinical research in South Asia has shown how improved regimens of atropine can prevent deaths. However, we are still unsure about which patients are most likely to benefit from the use of oximes. Supplemental antidotes, such as magnesium, clonidine and sodium bicarbonate, have all been proposed and studied in small trials without production of definitive answers. Novel antidotes such as nicotinic receptor antagonists, beta-adrenergic agonists and lipid emulsions are being studied in large animal models and in pilot clinical trials. Hopefully, one or more of these affordable and already licensed antidotes will find their place in routine clinical care. However, the large number of chemically diverse OP insecticides, the varied poisoning they produce and their varied response to treatment might ultimately make it difficult to determine definitively whether these antidotes are truly effective. In addition, the toxicity of the varied solvents and surfactants formulated with the OP active ingredients complicates both treatment and studies. It is possible that the only effective way to reduce deaths from OP insecticide poisoning will be a steady reduction in their agricultural use worldwide.

If Tatsuji Namba was to visit the medical wards of South Asia today, some 55 years after his pioneering work in Japan and the United States on occupational organophosphorus (OP) insecticide poisoning [1–3], he would feel very much at home. This is unfortunately a damning indictment on our efforts to improve treatment for this major public health and clinical problem that continues to kill as many as 200 000 people every year [4, 5].

Namba's work followed two key publications in 1955 [6, 7]. The first, by Freeman and Epstein, reported on the use of atropine as an anti-muscarinic treatment for the new cases of occupational OP insecticide poisoning that were then occurring in the United States. The second, by Wilson and Ginsburg, reported on the development of pralidoxime as an acetylcholinesterase (AChE) reactivating oxime drug, the treatment that Namba did so much to bring into clinical practice over the following decade. Unfortunately, little has changed since that time and patients presenting to hospital continue to be treated in similar ways, with atropine and oximes [8]. The only differences he would find are that: (i) the vast majority of severe cases now occur after ingestion of insecticides for self-harm, a problem that exploded in the 1970s and 1980s; (ii) resuscitation and supportive care is much improved; (iii) we know better how to use atropine; and (iv) we are much less confident about the clinical benefit offered by oximes.

Toxicity

OP compounds bind to and phosphorylate multiple enzymes and proteins throughout the body [9, 10]. However, the clinical relevance of the great majority of these interactions is currently unclear. Instead, it is the inhibition of synaptic AChE that appears to be pivotal for toxicity, resulting in accumulation of acetylcholine and overstimulation of acetylcholine receptors in the autonomic nervous system, central nervous system and neuromuscular junction (NMJ).

Severe toxicity results in acute respiratory failure due to reduced central respiratory drive, neuromuscular dysfunction and bronchorrhoea. Poisoning with rapidly active OP insecticides can result in respiratory arrest within 30 min; many patients therefore die before reaching medical care. Patients who do survive to hospital presentation require resuscitation; administration of oxygen, fluids and atropine; and ventilatory support [11]. Some deaths then occur acutely owing to cardiovascular shock with pesticides such as dimethoate [12]; others occur later during hospital admission, secondary to complications that occurred before hospital admission – for example, aspiration or hypoxic brain injury – or to NMJ dysfunction (the intermediate syndrome) that can require ventilation for days and sometimes weeks.

Unlike after OP nerve agent exposure [13], seizures appear to be uncommon after OP insecticide poisoning, occurring in just 1–3% of patients poisoned by World Health Organization (WHO) Class II compounds [12, 14, 15]. The mechanism of seizures is likely to be multifactorial, including hypoxia and the effects of excess acetylcholine on cholinergic synapses and then other neurotransmitter systems. Myocardial injury can occur after OP insecticide poisoning, with a recent study showing a modest rise in troponin I (median peak concentration 305 [interquartile range: 78–2335] ng l^{-1}) occurring in 34% of patients a median of 15 h post-poisoning [16]. Postmortem histology has shown myocardial interstitial oedema and patchy inflammation that might be due to OP insecticide, solvent, atropine treatment and/or hypoxia. Premortem echocardiography and the electrocardiogram (ECG) in these patients showed modest changes [17]. ECGs have often shown modestly prolonged QT intervals but these are typically taken on first admission, before administration of atropine, with the confounding effects of hypoxia, bradycardia and hypotension.

Organophosphate-induced delayed neuropathy (OPIDN) due to neuropathy target esterase inhibition can occur after several weeks, while extrapyramidal signs probably related to dopamine blockade have been reported [18].

Anti-muscarinic drugs

The muscarinic receptor antagonist atropine (Table 1) has been the core of antidotal treatment since the 1950s. It is a competitive nonspecific antagonist with good central nervous system (CNS) penetration, allowing it to be effective wherever muscarinic receptors are overstimulated by acetylcholine.

Glycopyrrolate is preferred by some clinicians because its poor CNS penetration produces less central anticholinergic toxicity in overdose. However, this also

Table 1

Pharmacological treatments available for organophosphorus (OP) poisoning

Drug name	Type	Dose	Reference
Atropine	Anti-muscarinic	•Give a bolus loading dose of 0.6 to 3 mg, rapidly IV •Then administer doubling doses every 5 min until the patient is atropinized (HR >80 bpm, SBP > 80 mmHg, clear lungs) •Once the patient is atropinized, give an infusion of 10–20% of the total dose required to atropinize the patient each hour in 0.9% saline chloride •Watch the patient carefully for recurrent cholinergic toxicity or onset of atropine toxicity (see below) •If cholinergic toxicity recurs at any point, restart the bolus doses until the patient is atropinized again and increase the infusion rate by 20% per hour •If the patient becomes atropine toxic (tachycardia, absent bowel sounds, hyperthermia, delirium, urinary retention), stop the infusion for 30 min and then start again at a 20% lower dose	[8, 25]
Pralidoxime	Oxime AChE reactivator	•Give a loading dose of 20–30 mg kg^{-1} over 30 min •This dose can be repeated at 6–8 h intervals •Alternatively, a continuous infusion of 5–10 mg kg^{-1} h^{-1} can be given in 0.9% sodium chloride •The duration of treatment is uncertain. Treatment can be stopped at 48 h and then restarted if clinical or electrophysiological deterioration occurs. Monitoring of red cell AChE activity can be helpful	[26, 28]
Obidoxime	Oxime AChE reactivator	•Give a loading dose of 250 mg over 30 min •Then give a continuous infusion of 750 mg every 24 h until clinical recovery	[26, 28]
Diazepam	GABA-A agonist	Give 10–20 mg IV to agitated patients or patients with impaired respiration for whom intubation and ventilation are available	[42]

Doses are given for the antidotes widely used for OP insecticide poisoning. The evidence for these doses is generally weak (see text). AChE, acetylcholinesterase; bpm, beats per minute; GABA, gamma-aminobutyric acid; HR, heart rate; IV, intravenously; SBP, systolic blood pressure.

makes glycopyrrolate a poor antagonist of the central effects of lipid-soluble OP insecticides, increasing the risks of seizures and coma. Furthermore, titrated-dose atropine is not associated with a high incidence of severe side effects [19]. A single underpowered randomized controlled trial (RCT) comparing glycopyrrolate with atropine found no difference in case fatality or need for intubation [20].

Nebulized ipratropium has been used in a single published case to complement intravenous atropine [21]. Scopolamine, instead of atropine, has been given to a woman with predominantly central features of chlorpyrifos poisoning [22].

Atropine dosing

Atropine is administered intravenously to restore adequate cardiorespiratory function rapidly – a process often termed 'atropinzation'. It is used to reverse bradycardia and improve systolic blood pressure to greater than 80 mmHg. At the same time, it aims to reduce bronchorrhoea, reverse bronchospasm and improve oxygenation; auscultation can be used to confirm the lack of wheeze and crepitations. Sweating is one of the first signs to resolve with atropine administration; by contrast, the reversal of pupil constriction can be delayed and should not be used to guide atropine administration. Excessive atropine results in antimuscarinic toxicity, with tachycardia, hyperthermia, absent bowel sounds, urinary retention, delirium, and ileus. Acutely, during resuscitation, excess atropine administration and toxicity are less important. However, patients should not be allowed to remain in this state after resuscitation, owing to the risk of increased agitation and cardiovascular collapse.

No dose–response studies have attempted to identify the ideal dosage regimen for atropine. A review of atropine dose regimens in the literature found 38 recommendations [23]. These varied markedly, administering a dose of 23.4 mg over 8–1380 min, and a dose of 75 mg over 25–4440 min. With many of these regimens, adequate resuscitation would be delayed for many hours. Atropinization was attained most rapidly with a regimen of sequentially increasing (doubling) bolus doses, titrated to effect. Once stabilized, patients received an infusion starting at about 20–30% of the starting dose, titrated against effect, and then increased and combined with bolus doses when found to be insufficient, or stopped and restarted at a lower rate if toxicity occurred.

First published in 2001 [24], this regimen was further recommended in 2004 [8]. A Bangladeshi RCT in 2006 tested whether this increasing dose regimen improved outcome compared with the repeat bolus dose regimen then in use [19]. This new regimen reduced the mean time for atropinization from 152 min to 24 min and was associated with a reduction in mortality from 22.5% to 8%, and is now the most widely recommended regimen [25]. Its adoption in the small peripheral hospitals that first see these patients will improve management and reduce deaths.

Oxime AChE reactivators

Pralidoxime (Table 1) has been used to treat OP insecticide-poisoned patients since the late 1950s. First used for patients occupationally exposed to highly potent WHO Class I toxicity insecticides, its administration appeared to result in clear clinical improvement and has been widely recommended ever since [26]. It is now the most commonly used oxime worldwide, typically as a chloride salt [27].

A second oxime, obidoxime, was developed in Germany during the 1960s; *in vitro* tests of human red-cell AChE reactivation showed that it is significantly more potent than pralidoxime [28]. There have been no formal comparative RCTs of obidoxime, yet its use is clearly associated with the reactivation of red cell AChE in case series of poisoned patients [29]. A small Iranian study of 22 OP insecticide-poisoned patients treated with obidoxime (8 mg kg^{-1} loading then 2 mg kg^{-1} h^{-1} infusion) reported liver toxicity in three patients, two of them fatal [30]. However, such liver toxicity has not been reported with the currently recommended obidoxime loading doses of 250 mg (~3.5 mg kg^{-1} in a 70 kg person) followed by 750 mg 24 h^{-1} (~0.45 mg kg^{-1} h^{-1}) [28, 31].

Other oximes, including trimedoxime, HI-6 and HLö-7, have been developed but have not yet been introduced into widespread clinical use. This is probably because their development has focused on OP nerve agent poisoning in industrialized countries rather than the much more common OP insecticide poisoning.

Oxime effectiveness

Oximes reactivate AChE, as shown by *in vitro* studies with human AChE, animal studies and observational clinical studies in humans [28]. However, there remains uncertainty about whether this efficacy translates into clinical benefit on the ward. The most recent Cochrane Collaboration review reported that there was insufficient evidence to determine whether oximes benefit patients [32], and pralidoxime was not selected for the WHO's Essential Drugs List in 2008.

Reasons for this apparent lack of effectiveness are multiple [28, 33]. The early studies of Namba looked at patients occupationally exposed to the highly potent WHO Class Ia toxicity OP, parathion. Relatively small amounts of this OP are required to cause severe

poisoning. As many WHO Class I toxicity pesticides have been banned, the majority of cases now concern the less potent WHO Class II OP insecticides, such as dimethoate and chlorpyrifos. Much larger doses of Class II pesticides are required to cause severe poisoning, such as seen with the intentional ingestion of whole bottles of pesticides; these quantities might simply overwhelm the dose of pralidoxime that can be administered. Patients can also take several hours to be transferred to a hospital where pralidoxime is available, resulting in its administration after irreversible ageing has occurred, reducing possible effectiveness. Finally, some of the toxicity might result from the large amount of solvents ingested in self-harm [34]. This toxicity will not respond to oxime therapy.

The first formal clinical studies of oximes in OP pesticide poisoning were performed in the early 1990s at the Christian Medical College, Vellore, India. These compared a relatively low-dose infusion of pralidoxime *vs*. a loading dose only [35] or placebo [36], and showed no evidence of reduced mortality {12 g infusion *vs*. 1 g bolus, 22% *vs*. 14%; odds ratio (OR) 1.77 [95% confidence interval (CI) 0.52, 6.0]; 12 g infusion *vs*. placebo, 29% *vs*. 5%; OR 7.1 [1.96, 26.0]}. At around the same time, De Silva and colleagues reported that a lack of pralidoxime in Sri Lanka hospitals for a 6-month period did not result in any increase in mortality [37]. However, these studies were criticized for using low doses of pralidoxime; higher doses were recommended [26, 38].

Two RCTs of high-dose regimens have been tested. The first, performed in Maharashtra, India, recruited 200 patients to a comparison of pralidoxime 1 g over 1 h *vs*. 1 g over 4 h for 48 h, both infused over 1 h and after a 2 g loading dose given over 30 min [39]. This study showed reduced mortality, from 8% to 1% [adjusted relative risk 0.11 (95% CI 0.01, 0.84)], as well as a reduced incidence of pneumonia and intubation postrandomization, and a reduced need for atropine and ventilation [39].

The second RCT, performed in the North Central province of Sri Lanka, recruited 235 patients to a comparison of a 2 g loading dose of pralidoxime over 20 min, followed by an infusion of 0.5 g h^{-1} for up to 7 days, *vs*. saline placebo [40]. This RCT was terminated early because of the publication of the Maharashtrian trial. It did not show reduced mortality, with 24.8% of patients receiving pralidoxime dying *vs*. 15.8% of patients receiving placebo (adjusted hazard ratio 1.69; 95% CI 0.88 to 3.26), or a reduced need for intubation. To reduce confounding due to the ingestion of different OP insecticides, a further analysis was performed of patients with laboratory-proven chlorpyrifos or dimethoate poisoning alone; again, this found no evidence of benefit [40]. Of note, uniquely, this study measured red cell AChE activity both before and after pralidoxime administration, finding clear reactivation in patients receiving pralidoxime and proving adequacy of dosage.

Both studies were performed in South Asia, and recruited patients poisoned by WHO Class II toxicity OP insecticides, but found different results. One major difference between the studies was the severity of illness, with moderate to severely ill patients being excluded from the Maharashtrian study, as shown by the lower mortality in the control arm (8% *vs*. 14%). By contrast, the Sri Lankan study recruited all patients who required atropine, thereby excluding only the 'least poisoned' patients. In addition, all Indian patients were routinely admitted to the intensive care unit of a private hospital, where they received one-to-one nursing care and intensive support. This differed considerably from the Sri Lankan study, which was performed in a government district hospital with few intensive care beds. The majority of these patients were treated, at least partially, on the open medical wards with a dearth of nursing and medical staff.

It is currently unclear whether there is a group of patients who will benefit clinically from pralidoxime administration. A series of small Phase II dose–response studies of the different oximes, measuring surrogate markers (e.g. AChE reactivation and neuromuscular function with electrophysiology) as well as clinical outcomes, is required to determine whether oximes might be beneficial to an identifiable subgroup of patients. In the meantime, sick patients should receive oximes in a critical care environment, with full support of airway and ventilation, plus titrated administration of atropine.

Benzodiazepines

Seizures are a relatively uncommon complication of OP insecticide poisoning [12, 14]. As for other toxicological seizures [41], benzodiazepines (Table 1) are recommended as first-line therapy [42]. Animal studies suggest that benzodiazepines might prevent OP nerve agent-induced brain damage [43]. However, whether such damage occurs after pesticide poisoning independently of overt seizures is currently unknown. Instead, benzodiazepines are recommended for the relief of agitation and anxiety in the poisoned patient.

Sodium bicarbonate

Blood alkalinization with sodium bicarbonate has been recommended by some for many years. The exact mechanism of possible benefit is unknown but might include enhanced OP clearance through pH-mediated hydrolysis, a direct effect on neuromuscular function or improved efficacy of oximes [44]. A few small RCTs have suggested a benefit [45, 46] but no large RCT has been performed and a Cochrane review found no evidence of benefit [44]. The risk of substantial side effects means

that this treatment will only be possible in a modern intensive care unit [47].

Magnesium sulphate

Magnesium reduces synaptic acetylcholine release by blocking calcium channels. Animal studies have suggested a benefit in reducing cholinergic stimulation after OP insecticide poisoning [48]. Magnesium might also reduce the risk of ventricular tachycardia in patients presenting with tachycardias due to nicotinic stimulation. Two very small clinical studies suggested an improvement in neuromuscular function [49] and reduced mortality [50], but the studies were not randomized and the methodology was unclear. A more recent Phase II dose–response study compared 4 g, 8 g, 12 g and 16 g of magnesium sulphate *vs*. placebo in groups of 10 OP insecticide-poisoned patients [51]. Magnesium sulphate at all doses was well tolerated and there was a trend towards reduced mortality with larger doses. A larger Phase II/III RCT is required.

Clonidine

Animal studies suggest that the central alpha-adrenergic agonist clonidine might be beneficial in OP insecticide poisoning by reducing synaptic acetylcholine release [52]. A single Phase II dose–response study has been performed to compare a loading dose of 0.15 mg, 0.3 mg or 0.45 mg clonidine, followed by an infusion of 0.5 mg over 24 h, *vs*. saline placebo [53]. The highest 0.45 mg dose of clonidine was associated with hypotension. No apparent effect on outcome was noticed; no larger RCT has since been performed.

Nicotinic receptor antagonist drugs

OP-induced NMJ dysfunction or intermediate syndrome causes patients to require mechanical ventilation for days or weeks [14, 54, 55]. Its pathophysiology is uncertain but is likely to be due to overstimulation of pre- and/or postsynaptic nicotinic acetylcholine receptors by excess acetylcholine, their downregulation and the failure of neurotransmission [55, 56]. Supportive ventilation is the only current therapy.

Atropine is given to poisoned patients to block muscarinic overstimulation. However, neuromuscular blocking agents (nicotinic acetylcholine receptor antagonists) are not currently used to prevent nicotinic overstimulation [57]. In a porcine model of OP poisoning, we found encouraging protective effects on NMJ function following early administration of rocuronium (Eddleston *et al*., unpublished observations). This suggests that the administration of neuromuscular blocking agents to patients already requiring ventilation for the predominantly central respiratory failure typical of acute cholinergic crisis might prevent subsequent nicotinic receptor overstimulation and NMJ dysfunction. A pilot RCT of this approach is currently underway in Sri Lanka (NCT02147054).

Beta-adrenergic agonists (salbutamol or albuterol)

Salbutamol might complement atropine during resuscitation by treating bronchospasm through beta-2 agonism. However, it might also work to increase fluid elimination from the lung. Poisoned patients' lungs become filled with fluid (bronchorrhoea) during acute cholinergic crisis, a clinical feature that is treatable with atropine. However, atropine only halts the production of fluid and does not speed its removal from the lung. A treatment that increases removal, complementing atropine's cessation of fluid production, could speed the return of effective oxygen exchange.

Although the mechanism is not fully understood, it might be similar to the alveolar fluid collection seen in the acute respiratory distress syndrome. Studies of fluid transport across the alveolar epithelium indicate that the epithelium is actively involved in oedema fluid clearance [58]. Upregulation of sodium transport with beta-adrenergic agonists such as salbutamol increases fluid egress in animal models. A nebulized dose of salbutamol – available in rural hospitals worldwide – might be able to access the alveolar epithelium and increase the rate of fluid removal in OP poisoning. If administered with atropine, the transient effect of nebulized salbutamol should not be detrimental as fluid production would have ceased with atropine administration by the time the effects of salbutamol had waned.

The recent Balti-2 study looked at the effect of 7 days of intravenous salbutamol in patients with established acute lung injury and showed no benefit [59]. However, this is unlikely to be relevant to poisoned patients because of the different route of administration (nebulized) and time course (given only during resuscitation over the first hour or so after presentation). The disadvantage of this route is that the pulmonary fluid might reduce the ability of salbutamol to access the alveolar epithelium. To gather initial pilot safety data, a small pilot study (NCT02160548) has been started in Bangladesh.

Lipid emulsions

Over recent years, the use of lipid emulsions for the treatment of severe cardiotoxicity has spread from bupivacaine to other cardiotoxins, including antipsychotic agents and

antidepressants [60]. The exact mechanism is unclear but proposed mechanisms include a direct effect on cardiomyocyte metabolism and an intravascular 'sink'. Whereas some clinicians are keen advocates [61], others are more cautious, calling for better quality clinical evidence before widespread adoption [62].

Lipid emulsion has been used for the treatment of the lipid-soluble surfactant cardiotoxicity seen in glyphosate poisoning [63]. It has also been proposed for OP insecticide poisoning [64] because some OP insecticides are highly lipid soluble and formulated in lipid-soluble solvents. However, a rodent study of unformulated parathion showed little benefit [65]. One case report suggested a benefit after parathion poisoning [66]. A formal Phase II/III RCT on this intervention is required.

OP hydrolases

An alternative approach to treating OP insecticide poisoning would be to enhance their hydrolysis in the blood, reducing toxicity and enhancing the effect of other antidotes. Research on medical countermeasures for highly potent chemical nerve agents, such as sarin and tabun, has focused on pretreating people with the mammalian enzymes butyrylcholinesterase and paraoxonase, sometimes in concert with oximes, to break down OP compounds in the blood after exposure [67]. However, butyrylcholinesterase is a stoichiometric inhibitor, binding on a one-to-one basis with the OP. As it is poorly reactivated by coadministered oximes [68], it will only be able to bind a single OP molecule, limiting its efficacy. Paraoxonase is enzymatic, and able to break down multiple OP molecules, but it is highly specific for its substrates [69], similarly limiting its usefulness.

Bacterial OP hydrolases have been isolated [70, 71] and shown after intravenous administration to be highly effective at breaking down a variety of OP insecticides in the blood [72]. Their immunogenicity will limit repeated administration in the short term, similar to streptokinase, but they might be useful for treating acutely poisoned patients. However, it is unclear whether the funds are available to develop such a treatment for this patient population and there appears to be little movement towards their clinical development.

Pesticide solvents

OP insecticides are commonly formulated with solvents and surfactants to enhance their agricultural uses. Of note, unformulated dimethoate does not reproduce the toxicity of formulated agricultural dimethoate in minipigs. This is the case, in spite of similar blood dimethoate/metabolite concentrations and AChE inhibition, suggesting that the combination of solvent (cyclohexanone) and dimethoate is essential to reproduce agricultural dimethoate toxicity [34].

However, solvents have never been studied in human OP poisoning. The solvent in the formulation varies by both manufacturer and OP insecticide, meaning that there are likely to be many combinations to which patients are exposed. It is possible that solvent toxicity might be responsible, in part, for the variation observed in outcome and the poor effectiveness of antidotes. Much more information is needed from clinical cases on the effect of solvents. Any harmful solvent could then be replaced in the formulation.

Conclusions

Although multiple antidotes have been proposed for the treatment of OP insecticide-poisoned patients, only a single antidote – the muscarinic receptor antagonist atropine – has clear evidence of efficacy and an undisputed role in management (Table 1). Oximes are widely used and recommended but with little high-quality RCT evidence of effectiveness. A programme of clinical pharmacology research is required to identify effective doses of these antidotes and the particular patient subgroups that might benefit from their administration. However, identifying effective antidotes is going to be complicated by the great variety of OP insecticides, affecting pharmacokinetics, time of toxicity onset and responsiveness to treatment. Furthermore, the presence of toxic coformulated solvents and surfactants – which vary according to brand and OP active ingredient – will confound clinical studies. It is possible that only a ban will prevent these deaths. If 200,000 people continue to die every year from OP insecticide poisoning, the time for this ban must be very near.

Competing Interest

Both authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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