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# Novel Clinical Toxicology and Pharmacology of Organophosphorus Insecticide Self-Poisoning

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## Keywords

insecticide, highly hazardous pesticides, organophosphate, suicide

## Abstract

Organophosphorus insecticide self-poisoning is a major global health problem, killing over 100,000 people annually. It is a complex multi-organ condition, involving the inhibition of cholinesterases, and perhaps other enzymes, and the effects of large doses of ingested solvents. Variability between organophosphorus insecticides—in lipophilicity, speed of activation, speed and potency of acetylcholinesterase inhibition, and in the chemical groups attached to the phosphorus—results in variable speed of poisoning onset, severity, clinical toxidrome, and case fatality. Current treatment is modestly effective, aiming only to reactivate acetylcholinesterase and counter the effects of excess acetylcholine at muscarinic receptors. Rapid titration of atropine during resuscitation is lifesaving and can be performed in the absence of oxygen. The role of oximes in therapy remains unclear. Novel antidotes have been tested in small trials, but the great variability in poisoning makes interpretation of such trials difficult. More effort is required to test treatments in adequately powered studies.

## INTRODUCTION

Organophosphorus (OP) insecticide self-poisoning or attempted suicide is the most important global form of acute poisoning, affecting over one million people each year and killing around 100,000 (1, 2). The introduction of these insecticides into global agricultural during the Green Revolution in the 1960s (3) brought them into poor rural communities that were completely unprepared to use or store them properly. Easy access to highly hazardous pesticides that are fatal after ingestion of small amounts transformed previously nonlethal self-poisoning into suicides. Suicide rates in countries such as Sri Lanka exploded as health care systems were simply unable to deal with these fast-acting poisons (4).

Prevention of OP self-poisoning will need to be multifaceted, involving regulation to remove the most hazardous pesticides from agricultural practice; the improved use and storage of pesticides, particularly by small-scale farmers; and improved medical management. Data from Sri Lanka (5) and Bangladesh (6) have shown that bans of the most highly hazardous OP insecticides [e.g., World Health Organization (WHO) Class I toxicity compounds (7) such as methyl parathion and monocrotophos] have resulted in remarkable reductions in overall suicide rates without overtly affecting agricultural yield or costs (6, 8). In Sri Lanka's case, these bans, in combination with bans of endosulfan and paraquat, have saved an estimated 93,000 lives over 20 years at a direct regulatory cost of USD 1.4 per life-year saved (5, 9). Many thousands of lives will be saved if such bans of highly hazardous OP insecticides are implemented worldwide (10).

Unfortunately, even where the highly hazardous Class I OPs have been banned, the case fatality for self-poisoning with WHO Class II insecticides such as dimethoate remains high, with 10–20% of people dying (11). More effective treatments are urgently required.

Although many millions of people have died from OP insecticide self-poisoning since the 1960s, the subject has gained relatively little attention (12). Instead, almost all research is focused on OP nerve agent chemical weapons such as sarin. Immense effort and funds go into finding novel antidotes for OP nerve agents, despite the relative paucity of cases and the huge human cost of insecticide self-poisoning.

## TOXICOLOGY AND CLINICAL COURSE

The pivotal mechanism of OP insecticide toxicity is inhibition of acetylcholinesterase (AChE) (EC 3.1.1.7) at cholinergic synapses across the central nervous system and autonomic nervous system, as well as at the neuromuscular junction (NMJ). An inability to break down acetylcholine results in overstimulation of muscarinic and nicotinic receptors and clinical features that include excess sweating, salivation, bronchospasm, bronchorrhea (pulmonary edema), bradycardia and hypotension, NMJ dysfunction, and reduced consciousness (13–15).

Patients die from respiratory failure due to a combination of a lack of central respiratory drive, NMJ dysfunction, and hypoxia from bronchorrhea. Patients who survive long enough to be hospitalized will need resuscitation with oxygen, fluids, and a muscarinic receptor antagonist (typically atropine). Many comatose patients require intubation and ventilation to maintain respiratory function.

The timing of acute respiratory failure, and therefore the likelihood of surviving to reach medical care, varies according to the dose and particular OP insecticide ingested (**Figure 1*a***). Patients ingesting very large doses or highly toxic pesticides will more rapidly inhibit a clinically significant proportion of their AChE and exhibit features earlier. Lipid solubility and the need for conversion to an active poison (see the section titled Organophosphorus Insecticide Chemistry) also likely affect the time to onset. Out-of-hospital cardiorespiratory arrest in most parts of the

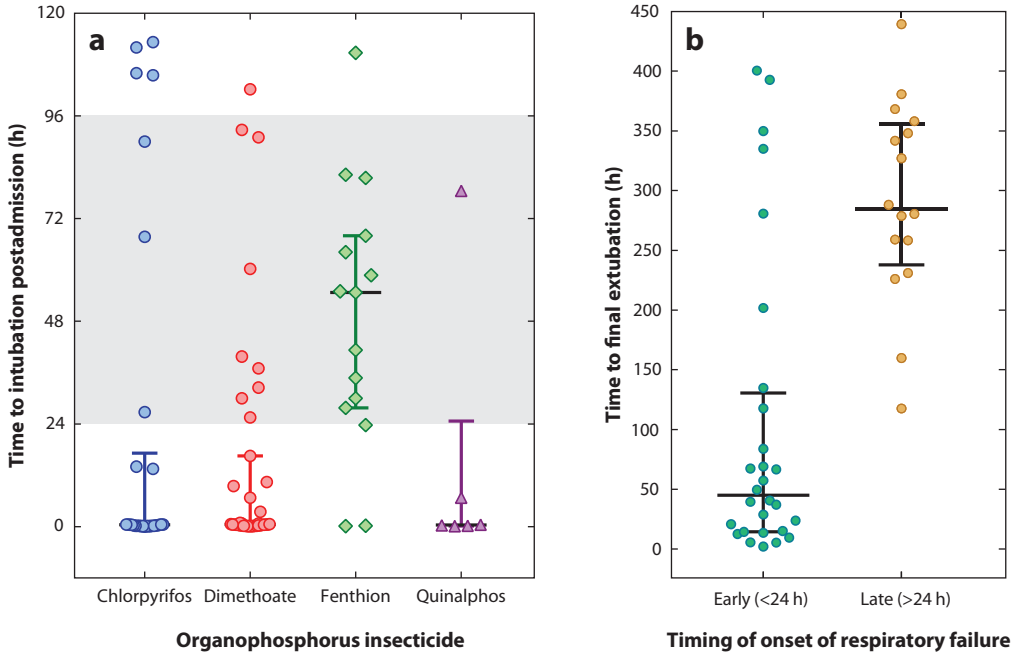



**Figure 1**

Intubation and extubation timelines for self-poisoning with several particular OP insecticides. (*a*) Time to first intubation according to OP insecticide ingested, showing marked differences between pesticides. The gray area indicates the 24–96 h period during which late respiratory failure (intermediate syndrome) is said to occur. However, some patients developed sudden respiratory failure both before and after this time period, up to 115 h postintubation. A large proportion of patients with chlorpyrifos, dimethoate, or quinalphos self-poisoning were intubated around admission. (*b*) Effect of the time to first intubation on the duration of ventilation. Patients intubated within 24 h of admission had a shorter time to final extubation compared to patients intubated after 24 h. In both panels, the bars show median (IQR) time. Abbreviations: IQR, interquartile range; OP, organophosphorus. Figure adapted from Reference 25 with permission from Oxford University Press.

world will result in the patient's death; in a Korean study, in a location with an effective emergency ambulance system, only 22% and 10% of insecticide-poisoned patients with an out-of-hospital cardiac arrest survived to admission and discharge, respectively (16).

Patients who reach a hospital in time to be intubated and ventilated may still die from OP poisoning (17, 18). High-dose dimethoate self-poisoning often results in death from cardiovascular shock that is resistant to atropine and vasopressors (11, 19), which may be due in part to the effect of solvents in combination with the OP active ingredient (see the section titled Solvent and Ethanol Coingestants). In addition, patients who become unconscious before hospital presentation may aspirate their stomach contents, resulting in aspiration pneumonia and/or acute respiratory distress syndrome, or they may suffer hypoxic brain injury from which they do not recover (20, 21).

Wadia et al. (22) and then Senanayake & Karalliedde (23) described a delayed respiratory failure, called type II respiratory failure or intermediate syndrome, respectively, occurring in conscious patients that seems to be due to NMJ dysfunction of particularly proximal muscles. This respiratory failure contrasts with that which occurs earlier in unconscious patients, where a loss of central respiratory drive is likely to be a major component (24). Patients with late respiratory failure (occurring after 24 h) often require ventilation for many days [in one study, for a median of 284 h compared to just 45 h for those intubated before 24 h (25)] (**Figure 1*b***), leaving them at

high risk of complications from immobility and mechanical ventilation. This delayed respiratory failure may occur after resolution of the acute cholinergic crisis, as originally described (23). It can also occur at the same time as the acute cholinergic syndrome and reduced consciousness (25); some patients effectively wake up from the central effects of the OP insecticide but continue to have a respiratory paralysis due to peripheral effects.

OP insecticides also inhibit the plasma enzyme butyrylcholinesterase (BuChE) (EC 3.1.1.8); however, this inhibition appears to have no substantial clinical effect beyond a potential small benefit from stoichiometric binding to the OP insecticide in plasma, lowering its concentration. There is also marked variation in the degree to which particular OP insecticides inhibit BuChE versus AChE (26), suggesting that BuChE inhibition is not a good marker of AChE inhibition, unless the specific OP is known.

## NOVEL TOXICOLOGY

Casida & Quistad (27, 28) have reported OP inhibition of a range of enzymes across multiple body systems in animal models. This inhibition, where investigated, does not appear to be important for acute rodent OP toxicity (see, e.g., 29). Their role has not yet been studied in poisoned humans, and it is possible that some may be of clinical relevance.

The OP insecticide chlorpyrifos potently inhibits brain monoacylglycerol (MAG) lipase activity, a key degrading enzyme of the endogenous endocannabinoid system (30). MAG lipase inhibition results in raised concentration of the cannabinoid agonist 2-arachidonoylglycerol (2-AG) in the brain, which is associated with hypomobility in rodents (31). A second endocannabinoid-degrading enzyme, fatty acid amide hydrolase (FAAH), is also inhibited by the OP insecticide profenofos, but its inhibition does not correlate with clinical effects (31, 32). Chlorpyrifos is a common WHO Class II OP insecticide responsible for many deaths worldwide (11, 33). Similar to all OP poisoning, chlorpyrifos is acutely associated with coma and paralysis; it is possible that raised 2-AG has a role in the coma. Human studies are required but will be complex due to the difficulty of measuring the activity of an enzyme (i.e., MAG lipase) that does not occur in the blood. Plasma cannabinoid concentrations can be measured, and increased concentrations in acute poisoning could be suggestive of reduced breakdown. However, plasma activity may not necessarily correlate with activity in the brain, the presumed site of key activity (31).

## ORGANOPHOSPHORUS INSECTICIDE CHEMISTRY

Many hundreds of OP insecticides were developed and introduced into global agriculture in the twentieth century. They vary in multiple important ways, including the degree of lipid solubility, the alkyl groups attached to the phosphorus, the rate of activation (conversion from thion to oxon), and the rate of AChE inhibition. These differences result in marked variation in toxicity, the speed of onset, and the clinical syndrome after ingestion (34). Fortunately, a smaller range of compounds is typically used for agriculture in any one area, reducing the variation in self-poisoning seen among patients.

OP insecticides vary widely in their lipid solubility. Some OP insecticides are relatively hydrophilic with log Kow (log P) values $<1.0$ [e.g., dimethoate (0.76) and trichlorfon (0.51)], while others are highly lipophilic with high log Kow values [e.g., chlorpyrifos (5.05), dichlofenthion (5.14), and profenofos (4.56)] (35). Lipophilicity markedly affects the volume of distribution, the acuteness of toxicity, and both the duration and recrudescence of toxicity, as shown in rat studies of trichlorfon and dichlofenthion (36). Poisoning with lipophilic insecticides results in relatively minor early clinical features, recurrence of toxicity, delayed respiratory failure, and prolonged

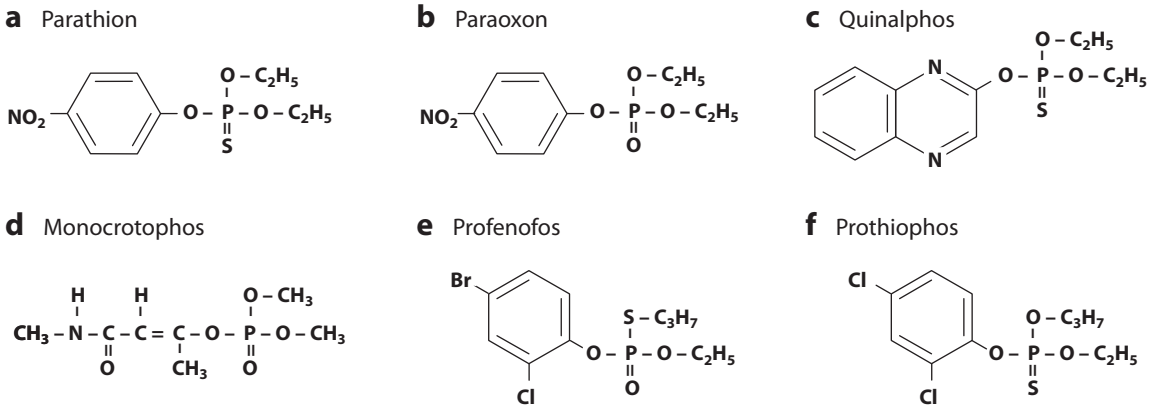



**Figure 2**

Structure of representative OP insecticides. The figure demonstrates (*a*,*c*,*f*) thions (P=S) and (*b*,*d*,*e*) oxons (P=O), as well as (*d*) dimethoxy, (*a*,*b*,*c*) diethoxy, and (*e*,*f*) S-alkyl OP insecticides. Figure adapted from Reference 34 with permission from Elsevier.



cholinesterase inhibition due to sustained delivery from fat stores to the systemic circulation (11, 25, 37). Poisoning with hydrophilic OP insecticides often produces relatively acute poisoning with rapid resolution if the patient survives (11).

In addition, the quantity of patient fat affects the outcome of poisoning with lipophilic OP insecticides. A Korean study of overweight patients [body mass index (BMI) > 25] showed a longer duration of ventilation, intensive care, and hospital admission after poisoning with highly lipophilic OP insecticides compared to nonlipophilic OP insecticides (38). This difference between highly lipophilic and nonlipophilic OP insecticides did not occur in patients with a BMI of 25 or less.

Many OP insecticides are propoisons (i.e., thions) (**Figure 2**), with a P=S structure that must be converted to a P=O (or oxon) structure to obtain effective cholinesterase inhibition. Thion OPs are activated by cytochrome P450 (CYP450) enzymes in the liver and intestinal mucosa. The precise CYP450s responsible vary according to the concentration of OP. For example, at low concentrations, chlorpyrifos, diazinon, parathion, and malathion are all metabolized and activated in vitro by CYP1A2 and 2B6 (39, 40). However, at the higher concentrations likely to occur from self-poisoning, CYP3A4 becomes dominant. The CYP450 enzymes involved in the metabolism of active oxons to inactive metabolites are less clear. The rates of conversion may determine the speed of inhibition and speed of onset of clinical features. However, this does not appear to always be a key rate-limiting step since a highly potent thion such as parathion, which must be converted in vivo to paraoxon, can induce clinical features, including coma and respiratory arrest, within 15–30 min of ingestion (41).

The speed of AChE inhibition itself may be a more important factor. In vitro studies have shown widely differing rates of inhibition by oxons, with fenthion, for example, being a slow inhibitor of AChE (39, 42). This relatively slow inhibition of AChE by fenthion and its slow conversion to fenthion oxon, more than its high lipid solubility (producing low extracellular fluid concentrations), may account for the much-delayed toxicity of fenthion compared to other lipid-soluble thion OP insecticides such as chlorpyrifos (**Figure 1*a***) (11, 25).

Most OP insecticides have either two methyl groups or two ethyl groups attached via oxygen atoms to the phosphorus atom, which produces dimethoxy or diethoxy OP compounds (**Figure 2**).

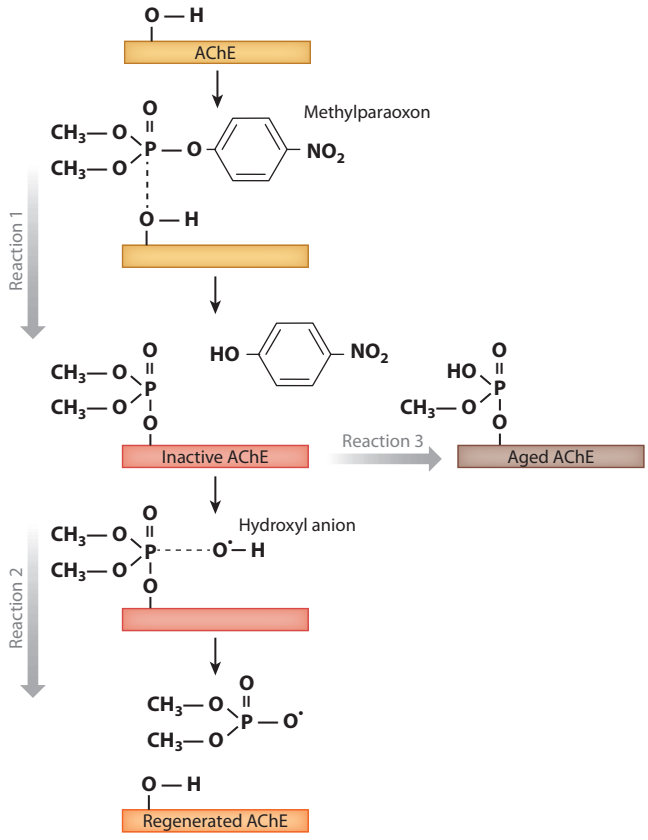



**Figure 3**

Inhibition, reactivation, and aging of AChE. A dimethoxy-phosphorylated OP oxon (methyl paraoxon) inhibits AChE by phosphorylating the serine hydroxyl group at the enzyme's active site (reaction 1). Active AChE is regenerated by a hydroxyl ion attacking the phosphorylated serine residue, which removes the phosphate moiety and releases active enzyme (reaction 2). Oximes speed up this reaction, ideally allowing reactivation to match the rate of inhibition; however, very high doses of OP insecticide will overwhelm oxime-induced reactivation. While in the inactive state, the enzyme is prone to the process of aging (reaction 3) in which one alkyl side chain of the phosphoryl moiety is removed nonenzymatically, leaving a hydroxyl group in its place and an aged AChE that can no longer be reactivated. Abbreviations: AChE, acetylcholinesterase; OP, organophosphorus. Figure adapted from Reference 44 with permission from Oxford University Press.

Binding to, and the inhibition of, AChE results in the production of either dimethoxy-phosphorylated or diethoxy-phosphorylated AChE (**Figure 3**), irrespective of the actual OP insecticide involved. A few are S-alkyl OP insecticides (**Figure 2*e*,*f***) in which one of the alkyl groups is attached to the phosphorus via a sulfur atom. This chemistry has major implications for the speed of aging and therefore the efficacy of oxime treatment.

Although the splitting of the choline–enzyme bond in normal acetylcholine metabolism is completed within microseconds, the severing of the OP compound–enzyme bond is prolonged. The half-life of this reaction depends on the chemistry of the substituted phosphate. The in vitro half-life for spontaneous reactivation of human AChE inhibited by dimethoxy OPs is 0.7–0.86 h, and 31–57 h for diethoxy inhibition (43). Spontaneous reactivation is therefore quicker with

dimethoxy OPs; however, this is only clinically relevant in patients with more moderate OP toxicity because the reactivated AChE is simply reinhibited again in patients with high OP concentrations.

Dimethoxy-phosphorylated AChE ages faster than diethoxy-phosphorylated AChE (**Figure 3**), meaning that it rapidly becomes unresponsive to oximes with a half-life of 3.7 h (versus 33 h for diethoxy) (44). A delay of 4 h to oxime therapy will mean that 50% of AChE is already irreversibly inhibited. Oxime therapy may be effective for several days with diethoxy OP insecticides. Aging of AChE inhibited by S-alkyl OP insecticides appears to occur very quickly, allowing no response to oximes, even if given early (45).

OP insecticide toxicity may also be increased in the bottle, before ingestion, by chemical reactions resulting from storage at warm temperatures (46). In a large Pakistani epidemic, the conversion of malathion to the more toxic compound isomalathion in the bottle correlated with increased toxicity (47). Increased toxicity has also been noted after the prolonged storage in warm conditions of diazinon (48) and dimethoate (49).



## SOLVENT AND ETHANOL COINGESTANTS

A person who drinks an agricultural OP insecticide is ingesting not only the active OP ingredient but also the chemicals with which the active ingredient has been formulated. Self-poisoning worldwide is most commonly done with an emulsifiable concentrate (EC) liquid formulation (50) for agricultural use that is bought from a shop. The insecticide has been designed to be mixed with water, requiring a solvent, such as xylene, cyclohexanone, or petroleum distillates, and a surfactant.

The solvents used in OP insecticides vary by brand. Different brands of a single OP insecticide may have different solvents; at the same time, similar solvents may be used for multiple OP insecticides made by a single company. The concentrations of these compounds are often high—many formulations are 40% OP active ingredient together with 40–60% solvents. For example, dimethoate EC40 consists of 40% dimethoate, 40% cyclohexanone, and 5% xylene as well as a surfactant.

The effect of ingesting large doses of solvents in OP insecticide self-poisoning is likely to be significant. A porcine study showed that neither the dimethoate active ingredient nor the cyclohexanone solvent, in quantities matching the parent formulation, was alone sufficient to reproduce the cardiotoxicity seen in poisoned humans (51). However, poisoning with the same quantities of dimethoate and cyclohexanone together did reproduce the toxicity. Replacement of the cyclohexanone with another solvent resulted in a less toxic product.

The importance of solvents to human poisoning is not yet clear. Xylene and petroleum distillates have been detected in the urine of OP-poisoned patients (52) and at high concentrations postmortem (53–55), and such solvents can produce neurotoxicity (56). However, most importantly, there have been at least three reports (57–59) of self-poisoning with OP or carbamate insecticides formulated with methanol. This toxic alcohol is itself highly neurotoxic and requires antidotal therapy as well as hemodialysis for the quantities that may be drunk from a pesticide bottle (60). If OP insecticides are commonly formulated with methanol, then many cases of OP poisoning may actually be mixed methanol and OP poisoning. A large Korean study showed that a raised anion gap, not due to lactate, upon hospitalization was associated with a poor outcome (61). However, this study assessed all pesticides, including paraquat; there were no data specifically on OP insecticides and the role of solvents in raising the anion gap.

Another important coingestant is ethanol. Many patients, particularly men, ingest alcohol around the time of poisoning (62, 63), and high doses of ethanol may induce coma and exacerbate respiratory failure. In a prospective study of self-poisoning with dimethoate EC40, alcohol ingestion was associated with the ingestion of larger amounts of pesticide and a worse outcome

(64). However, a higher blood ethanol concentration, independent of the plasma dimethoate concentration, was not associated with worse outcome. A retrospective study of 135 OP insecticide–poisoned patients also reported that alcohol coingestion was associated with a worse outcome and that blood ethanol concentration correlated with higher ingested doses of OP insecticide (65). Using receiver operating characteristic analysis, the researchers identified a blood alcohol concentration of 173 mg/dL that was independently associated with death [odds ratio 4.9 (1.5 to 16.7)]. This independence differs from the dimethoate study in which controlling for the dimethoate concentration removed any association with alcohol, indicating that the effect of ethanol was due to higher doses of ingested OP and not the ethanol itself.

Further clinical studies, with accurate measurement of all elements of the formulation and ethanol in the plasma, are required to address the importance of coformulants in human self-poisoning.

## CLASSICAL TREATMENT OF ORGANOPHOSPHORUS INSECTICIDE POISONING

The primary cause of death after anticholinesterase poisoning is respiratory failure and hypoxemia resulting from muscarinic effects on the cardiovascular and pulmonary systems (i.e., bronchospasm, bronchorrhea, aspiration, bradydysrhythmias, or hypotension), nicotinic effects on skeletal muscles (i.e., weakness and paralysis), loss of central respiratory drive, and seizures (rare).

Therefore, initial treatment for a patient exposed to OP compounds should be directed at ensuring an adequate airway, oxygenation, and ventilation and at stabilizing cardiorespiratory function by reversing excessive muscarinic effects (34, 66). Once the patient is stable, the administration of an AChE-reactivating oxime drug, such as pralidoxime or obidoxime, can be considered along with the need for skin and/or gastric decontamination.

### Atropine

The use of atropine in OP insecticide poisoning has been accepted practice since the 1950s (67, 68); however, the preferred regimen has been clarified only recently. Atropine must be administered until the features of the acute cholinergic syndrome have settled: In particular, the bronchorrhea must be resolved and the lungs clear (while being aware of focal consolidation due to aspiration that will not resolve with atropine), the heart rate adequate (around 80 beats/min), and the blood pressure adequate (a systolic blood pressure greater than 80–90 mm Hg). This status is referred to as being atropinized. Unfortunately, such doses of atropine do not counter the central loss of respiratory drive or NMJ dysfunction; therefore, most severely poisoned patients require intubation and mechanical ventilation.

A systematic review of treatment guidelines in 2002–2003 found 33 different recommendations for administering atropine to resuscitate an OP insecticide–poisoned patient (69). Most recommended a range of fixed atropine doses (e.g., 2–5 mg) given every 5–15 min without titration to effect. Comparing the time to give 23.4 mg, the median dose in a Sri Lankan cohort of patients, the different regimens took from 8 to 1,380 min. Several regimens took more than 4 h to give sufficient atropine to stabilize patients. Administration of the high doses needed by some patients required many hours, while leaving the patients dangerously unstable. In the systematic review, one regimen stood out—that of Cynthia Aaron (70), who recommended giving 1–2 mg initially and then doubling the dose every 5 min in the absence of a response. This regimen took only 15 to 20 min to give 23.4 mg, could give much higher doses quickly if required, and was titrated to effect.

This regimen was incorporated into a clinical guideline (66) and is now recommended in the majority of guidelines worldwide (71) following a randomized controlled trial (RCT)

performed in Bangladesh (72). This RCT tested the standard therapy (2–5 mg every 10–15 min, followed by an infusion) with Aaron's regimen (1.8 to 3 mg every 5 min, doubled until atropinization occurred, followed by an infusion) in 156 patients with acute OP insecticide self-poisoning. Most importantly, the doubling dose regimen resulted in an 84% reduction in the mean time to atropinization, from 152 min to 24 min, with only a modest increase in total dose of atropine required (72). This much faster resuscitation was associated with a fall in case fatality from 22.5% to 8.0% and a reduction in the proportion of patients showing atropine toxicity from 28.4% to 12%.

After initial loading, atropine should be continued as an infusion titrated against cholinergic features. The infused dose can often be reduced to around 1 mg/h after several hours (73). Patients should thereafter be carefully and frequently observed for evidence of (*a*) deteriorating neurologic function and potential paralysis requiring ventilation and (*b*) either recurrent cholinergic signs (15) suggestive of inadequate atropine dosing or atropine toxicity (74) indicative of a need to reduce atropine dosing.

One concern in the rural Asian district hospitals where the majority of patients are seen is the intermittent supply of oxygen. For many years, guidelines have indicated that patients should not receive atropine until hypoxia has been treated with oxygen due to the risk of inducing ventricular tachydysrhythmias (68, 75). Unfortunately, many of these hospitals do not have easy access to oxygen. At the same time, atropine is effective at treating hypoxia by reversing bronchorrhea and bronchospasm. A review of the data cited in the guidelines revealed just two case reports, of debatable relevance, of cardiotoxicity associated with atropine (75). A large Sri Lankan case series in which patients received atropine on admission, whether oxygen was available or not, demonstrated no evidence of fatal atropine-induced dysrhythmias in such patients (75). Ventricular dysrhythmias were observed to occur late in 10% of a small German case series; however, the dysrhythmias resolved with atropine therapy (73).

Overall, these guidelines have caused unnecessary confusion, impeded good clinical care, and are not evidence based. Atropine can be given, if clinically necessary, before oxygen becomes available.

## Oximes

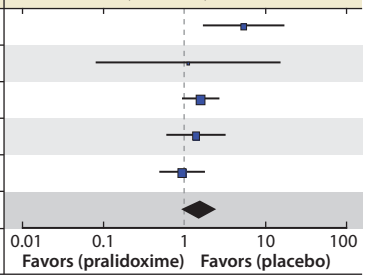
In the 1950s, groups in the United States and United Kingdom developed pralidoxime, a drug that reactivated AChE inhibited by OP compounds. Initially, it was used for occupational poisoning with high-potency (WHO Class I) diethoxy OP insecticides such as parathion (76, 77). For such poisonings with diluted insecticide, solvents and other coformulants are not relevant. Patients treated with 1 g of pralidoxime showed good reactivation of red blood cell AChE and clinical recovery, leading to recommendations that it be used for all OP insecticide–poisoned patients (68).

However, clinicians quickly recognized that much larger doses than 1 g might be needed for patients with intentional overdoses, who drink large quantities of OP in combination with solvents, particularly for less toxic WHO Class II pesticides such as malathion where large quantities need to be ingested to elicit moderate-severe poisoning (78). Namba et al. (78, 79) recommended doses of 0.5 g/h after a loading dose for such high-dose poisoning. However, this advice did not appear in guidelines and most patients over the following decades received 1 g every 6 h for 1–2 days.

An observational study performed in 1991 reported that the absence of pralidoxime for 6 months in Sri Lanka was not associated with worse outcomes, suggesting a lack of clinical effect (80). Advocates responded that higher doses, akin to Namba et al.'s high-dose regimen, should be given to all patients (81). WHO guidelines that were published in 2000 reinforced the view (82). However, in vitro studies with human red blood cell AChE and clinical studies of AChE

**Table 1 Meta-analysis of the effectiveness of pralidoxime chloride for preventing death in organophosphorus insecticide–poisoned patients**

| Study or subgroup | Treatment group (2-PAM) Events | Treatment group (2-PAM) Total | Placebo group Events | Placebo group Total | Weight (%) | Risk ratio M-H, random, 95% CI | Year | Risk ratio M-H, random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Cherian et al. (129) | 16 | 55 | 3 | 55 | 13.7 | 5.33 [1.65, 17.27] | 1997 | |
| Cherian et al. (130) | 1 | 10 | 1 | 11 | 3.5 | 1.10 [0.08, 15.36] | 2005 | |
| Eddleston et al. (91) | 30 | 121 | 18 | 114 | 33.2 | 1.57 [0.93, 2.66] | 2009 | |
| Banerjee et al. (131) | 11 | 60 | 8 | 60 | 21.5 | 1.38 [0.60, 3.18] | 2011 | |
| Syed et al. (132) | 13 | 50 | 14 | 50 | 28.1 | 0.93 [0.49, 1.77] | 2015 | |
| **Total (95% CI)** | | **296** | | **290** | **100.0** | **1.54 [0.92, 2.56]** | | |
| Total events | 71 | | 44 | | | | | |




Heterogeneity: $T^2 = 0.13$; $\chi 2 = 6.89$, $df = 4$ ($p = 0.14$); $I^2 = 42\%$. Test for overall effect $Z = 1.66$ ($p = 0.10$).
Abbreviations: 2-PAM, pralidoxime chloride; CI, confidence interval; M-H, Mantel-Haenszel. Table adapted from Reference 88 with permission from Springer.



inhibition indicate that the reactivation by oximes of AChE inhibited by dimethoxy or S-alkyl OP insecticides is much less effective than the reactivation of diethoxy OP insecticides (see the section titled Organophosphorus Insecticide Chemistry) (83, 84).

Treatment with oximes of poisoning with the dimethoxy thion OP dimethoate additionally seems to be even less effective than expected (11, 34). This may be due to the production of isodimethoate (85) in the pesticide bottle, when stored in hot conditions, before ingestion by the patient, producing an S-alkyl OP that is resistant to oximes.

These findings indicate that oximes are unlikely to be effective for many patients who are poisoned by dimethoxy or S-alkyl OP insecticides. Oximes may also be ineffective for all OP insecticide poisoning cases if the concentration of pesticide in the body is very high, overwhelming the capacity of oximes to reactivate AChE (86).

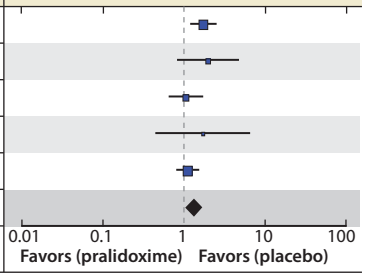
Systematic reviews of clinical trials of pralidoxime, including high-dose regimens (infusions of 0.5 g/h after a loading dose), compared with placebo support the idea that it does not prevent death or intubation (**Tables 1** and **2**) or shorten the duration of ventilation (87, 88). Of note, several of these studies included high-dose infusions for up to 7 days without benefit (89), indicating that inadequate dosing (81, 86) is not responsible for the lack of effect. The lack of efficacy may be due to the very large doses of OP insecticide ingested during self-harm. For example, a typical ingested dose of 100 mL of a 40% parathion formulation contains 40 g of active ingredient. This equals 666 mg/kg parathion for a 60-kg adult, a dose 51-fold greater than the rat oral median lethal dose for parathion of 13 mg/kg (7). The clinically tolerated doses of oxime may be unable to counter such huge doses, with any reactivated oxime simply being rapidly inhibited again by the high blood OP concentration (44).

An RCT of 200 OP-poisoned patients compared two pralidoxime regimens [2 g loading dose over 30 min followed by either 1 g pralidoxime (over 1 h) every 4 h for 2 days (total dose 14 g) or an infusion of 1 g/h for 2 days (total dose 50 g)], showing decreased mortality (90). It is unclear how these data complement the placebo-controlled data, especially since the patients were less severely poisoned than in other studies and a large proportion were intubated at baseline and cared for in an intensive care unit [66% versus, for example, 17% in a Sri Lankan RCT (91)].

Some groups have reported a benefit by titrating pralidoxime dosing against BuChE reactivation (92, 93). However, OP insecticides inhibit BuChE to variable degrees (26), and AChE

**Table 2 Meta-analysis of the effectiveness of pralidoxime chloride for preventing intubation in organophosphorus insecticide–poisoned patients**

| Study or subgroup | Treatment group (2-PAM) Events | Treatment group (2-PAM) Total | Placebo group Events | Placebo group Total | Weight (%) | Risk ratio M-H, random, 95% CI | Year | Risk ratio M-H, random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Cherian et al. (129) | 37 | 55 | 22 | 55 | 31.0 | 1.68 [1.16, 2.44] | 1997 | |
| Cherian et al. (130) | 7 | 10 | 4 | 11 | 7.6 | 1.93 [0.80, 4.64] | 2005 | |
| Eddleston et al. (91) | 26 | 121 | 24 | 114 | 20.6 | 1.02 [0.62, 1.67] | 2009 | |
| Banerjee et al. (131) | 5 | 60 | 3 | 60 | 3.2 | 1.67 [0.42, 6.66] | 2011 | |
| Syed et al. (132) | 31 | 50 | 29 | 50 | 37.6 | 1.07 [0.78, 1.47] | 2015 | |
| **Total (95% CI)** | | **296** | | **290** | **100.0** | **1.29 [1.00, 1.66]** | | |
| Total events | 106 | | 82 | | | | | |




Heterogeneity: $T^2 = 0.02$; $\chi^2 = 5.05$, $df = 4$ ($p = 0.28$); $I^2 = 21\%$. Test for overall effect $Z = 1.99$ ($p = 0.05$).
Abbreviations: 2-PAM, 2-pyridine aldoxime methyl chloride; CI, confidence interval; M-H, Mantel-Haenszel. Table adapted from Reference 88 with permission from Springer.



inhibition may differ from BuChE inhibition (34). A pralidoxime 2 g dose variably reactivated BuChE in patients who were poisoned by two WHO Class II diethoxy OP insecticides, chlorpyrifos and quinalphos; however, unlike AChE reactivation, the BuChE reactivation was not sustained (94). This dose did not reactivate BuChE inhibited by the dimethoxy OPs dimethoate or fenthion at all. A pralidoxime 1 g dose produced no reactivation with any OP insecticides (94). This suggests that titrating pralidoxime dosing against BuChE reactivation is unlikely to be effective, unless perhaps the particular OP ingested and its pharmacodynamics are known.

Although pralidoxime has been the key oxime used worldwide since the 1960s, there are other more potent oximes such as obidoxime and trimedoxime (43, 86). Lower concentrations of these oximes are required to reactivate human red blood cell AChE ex vivo (43); however, aging still occurs, indicating the need for early therapy. Although careful observational data have been reported for obidoxime treatment of OP insecticide self-poisoned patients showing clinical improvement (41, 73), there are no clinical trial data showing clinical effectiveness.

### Benzodiazepines

Benzodiazepine γ-aminobutyric acid (GABA) agonists such as diazepam or midazolam are recommended to settle agitation, prevent or treat seizures, and reduce fasciculations (95). Animal studies of OP nerve agent poisoning indicate that they can also prevent neuronal damage (96, 97); however, the relevance of this pathology to human poisoning remains unclear (95). Although they are a classically described feature of OP insecticide poisoning (13, 98), overt seizures are uncommon (1–3%) in hospitalized adult patients (11, 22), perhaps due to effective atropinization (99). Seizures may be more common in children (100, 101). No clinical trials have assessed whether benzodiazepine administration in OP insecticide self-poisoning offers clinical benefit (95).

## NOVEL TREATMENTS FOR ORGANOPHOSPHORUS INSECTICIDE POISONING

Current therapy is based on two treatments that were first reported in the 1950s. Many more possible therapies have been tested in animals; a few have made it into small, inadequately powered

clinical studies (102). There is an urgent need to find additional treatments that can complement and augment the often inadequate current therapy.

## Magnesium Sulfate and Calcium Channel Blockade

The use of magnesium or calcium channel blockers (CCBs) such as nifedipine in OP compound poisoning has long been advocated (103, 104). The precise mechanism of how this intervention might work remains unclear. Calcium is required in the presynaptic terminus for the exocytosis of acetylcholine to occur. Interruption of the calcium flow through channels by magnesium or CCBs may be sufficient to reduce the synaptic concentration of acetylcholine. OP insecticides also inhibit $Ca^{2+}$ ATPase, the enzyme responsible for removing cytosolic $Ca^{2+}$ (105). Rat studies suggest that CCBs reactivate OP-inhibited $Ca^{2+}$ ATPase, decreasing intracellular $Ca^{2+}$ concentrations and theoretically reducing acetylcholine release.

Administration of CCBs or magnesium to rodents before or soon after OP exposure, in addition to atropine and/or oxime, reduces mortality (reviewed in 106). A nonrandomized Iranian clinical study of 4 g magnesium sulfate ($MgSO_4$) in acute OP poisoning during 2003–2004 suggested that it was effective in reducing mortality and length of hospital stay (107). A total of eight clinical studies or trials have now been performed (441 patients; 239 patients receiving $MgSO_4$, 202 control patients; $MgSO_4$ doses up to 26 g/day), all of small-to-modest size and with marked risk of bias. The pooled odds ratios for $MgSO_4$ for mortality and need for intubation and ventilation for all eight studies were 0.55 [95% confidence interval (CI), 0.32–0.94] and 0.52 (95% CI, 0.34–0.79), respectively (106). This result suggests that this intervention might be beneficial, but it is far from definitive due to the size of the RCTs and the risk of bias. A large RCT is required to provide clear evidence.

## Sodium Bicarbonate for Plasma Alkalinization

OP insecticide poisoning often causes a metabolic and respiratory acidosis due to hypotension, hypoxia, and hypoventilation. This usually settles with fluid resuscitation, oxygen, atropinization, and mechanical ventilation. However, clinicians have proposed that sodium bicarbonate should be used as an antidote for OP insecticide poisoning to alkalinize the plasma (108, 109), as is done routinely to treat sodium channel blockade in tricyclic antidepressant poisoning (110). The proposed mechanism of effect is poorly defined but may include enhanced pesticide clearance from the body, improved efficacy of oximes, and a direct effect on NMJ function (111).

A systematic review of the literature identified only five low-quality clinical studies that together suggested a possible benefit from plasma alkalinization (111). However, attempts to study the approach in Sri Lankan district hospitals with few intensive care resources indicated difficulty in resource-poor hospitals that were inexperienced in giving bicarbonate (112). Further studies are required to understand whether it benefits patients and how it could be used in low-income countries that see the majority of patients.

## Salbutamol

OP insecticide poisoning is characterized by bronchorrhea and noncardiogenic pulmonary edema, which hinder oxygen exchange. Adequate atropinization turns off the fluid production, but it does not increase the removal of fluid from alveoli. A complementary therapy that increases fluid removal from alveoli could speed up the return of effective oxygen exchange and resuscitation. Salbutamol accelerates alveolar fluid clearance by enhancing salt and water transfer across alveolar and distal airways (113). It may also reverse OP insecticide–induced bronchoconstriction, thereby

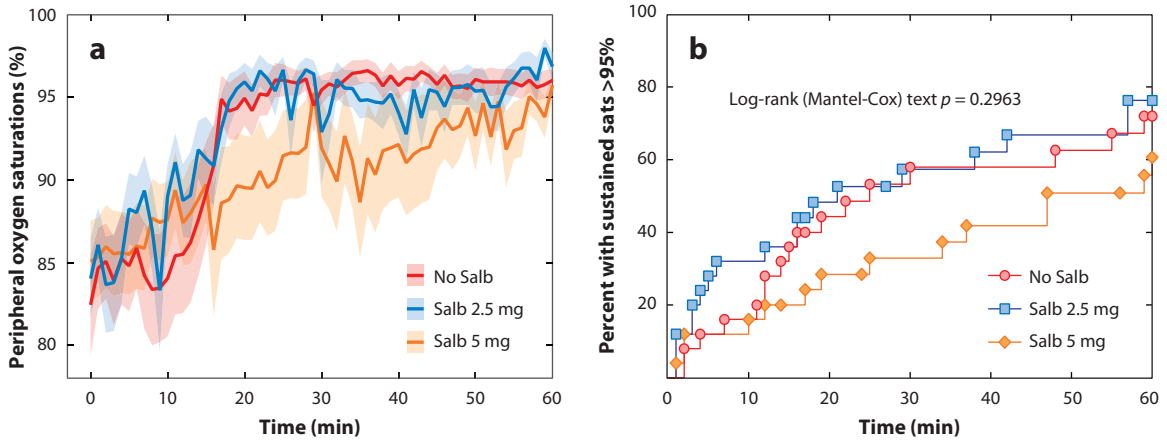



**Figure 4**

Effect of nebulized salbutamol on peripheral blood oxygen saturations in OP insecticide self-poisoned patients. (*a*) Mean (SEM) oxygen saturations of patients receiving no salbutamol (No Salb, *red*), 2.5 mg salbutamol (Salb 2.5, *blue*), and 5 mg salbutamol (Salb 5, *orange*) over the first 60 min of resuscitation. (*b*) Survival analysis of time to sustained oxygen saturations >95% for the three groups. Abbreviations: OP, organophosphorus; Salb, salbutamol; SEM, standard error of the mean. Figure adapted from Reference 115 with permission from Taylor & Francis.

improving respiratory mechanics by decreasing airflow resistance and peak airway pressures as well as increasing dynamic compliance (114).

A small phase II dose-response study was performed in a resource-poor hospital in Bangladesh to explore the effects of nebulized salbutamol (115). OP insecticide–poisoned patients ($n = 75$) requiring atropine for cholinergic features received a single 2.5 or 5 mg dose of salbutamol, or saline placebo, and their peripheral blood oxygen saturations were monitored every minute for 60 min. A mild tachycardia occurred in response to the higher dose of salbutamol, suggesting absorption. Oxygen saturations did not improve with the salbutamol (**Figure 4**). Indeed, recovery had already occurred by 20 min after placebo, and the higher dose was associated with a longer time to oxygen saturations that were consistently >95% (115). It is possible that this negative finding was due to the inevitable variation between patient groups seen in this small RCT; however, the results do not encourage additional studies in light of the other possible treatments.

## Nicotinic Antagonists

A key problem with OP insecticide poisoning is the NMJ dysfunction (intermediate syndrome) that may occur hours or days after exposure (17, 116). The mechanism is uncertain; however, it occurs in the face of adequate atropinization, suggesting a nonmuscarinic effect. The main mechanism proposed is overstimulation of post- and/or presynaptic nicotinic receptors at the NMJ (23, 117). A competitive nicotinic blockade, with a drug such as rocuronium, may prevent this overstimulation and damage (118). Phase II studies are required to explore the best way to give nicotinic antagonists to OP-poisoned patients.

## Lipid Emulsions

Lipid emulsions have been widely recommended for acute poisoning with lipid-soluble poisons, although the evidence and rationale are weak for treatment of oral overdoses rather than

intravenous local anesthetic overdoses (119, 120). Many OP insecticides are lipid soluble, and it is possible that intravenous lipid emulsions may redistribute the poison (121), but they may also increase absorption from the gut, thereby increasing toxicity. A rodent study has suggested that there may be a benefit from this treatment (122). Similarly, an uncontrolled study of 40 patients, published in abstract form, also suggested some benefit compared to historical controls (123). However, a recent in vitro study has suggested that the lipid emulsion may actually stabilize the OP from degradation (124). More studies are required to identify whether the approach is associated with a benefit for certain OP insecticides and/or worse toxicity before it can be used outside a clinical trial.

### Acetylcysteine

Oxidative stress has been reported in OP insecticide poisoning, likely due to initial hypoxia and tissue hypoperfusion. However, some researchers have proposed that oxidative stress is causal for poor outcomes rather than being associated with severe poisoning (125, 126). Acetylcysteine has been tested as a treatment for rodents (126) and in small, underpowered RCTs (127, 128). Again, larger RCTs are required before its clinical use.

## CONCLUSIONS

OP insecticide self-poisoning is a complex multi-organ condition, which involves inhibition of cholinesterases and perhaps other enzymes, and large solvent doses. Current treatment is not very effective—around 100,000 people die each year—and aims only to reactivate AChE and counter the effects of excess acetylcholine at muscarinic receptors. Bans of OP insecticides and formulation changes will rapidly reduce the number of deaths (10). However, in the near future, widespread use of cheap OP insecticides will continue in agriculture, facilitating millions of cases of self-harm, all requiring much more effective therapy than is currently available.

More effort must go into better understanding the pivotal pathology of the poisoning, including solvents, since this may reveal more therapeutic avenues. Greater effort is also required in setting up multiple phase II studies to understand how a therapy might work and then designing and funding large RCTs that can provide definitive data. Unfortunately, the great variability in self-poisoning—patients ingesting variable doses of different OP insecticides with differing properties and differing solvents and being hospitalized at variable times after exposure—means that phase II clinical trials will always be heterogeneous at baseline and difficult to interpret. RCTs will need to be large to counter this variation. A serious effort is required to give OP insecticide self-poisoning the clinical attention it deserves (12) and to set up high-quality RCTs wherever OP insecticide self-poisoning is an important clinical problem.

## DISCLOSURE STATEMENT

The author is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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**Errata**

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