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Organophosphate Poisoning With Delayed Intermediate Syndrome: A Narrative Review

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ABSTRACT

Organophosphate pesticide poisoning is a leading cause of death from self-harm in rural parts of the world, and survivors of the first cholinergic crisis can still die or be ventilated for days because of a second problem, the intermediate syndrome. First described in the 1970s and named in 1987, this syndrome appears after the acute features have settled and is marked by weakness of the neck flexors, proximal limb muscles, muscles supplied by cranial nerves and, most dangerously, the muscles of breathing. This narrative review describes what the published literature says about its recognition, its probable mechanisms, the compounds and treatment patterns associated with it, and its place among the other neurological consequences of organophosphate exposure. It reports no patient data and no new analysis. The evidence shows a clear clinical picture but a weak causal story: prolonged inhibition of acetylcholinesterase and changes at the nicotinic receptor are plausible, yet no single mechanism has been proved, and the effect of oxime and atropine regimens on its occurrence remains contested because the trials are small, differ in design and use varied definitions. Prospective cohorts suggest the syndrome is better thought of as a spectrum than as an all-or-nothing event, which makes incidence figures hard to compare. The review concludes that planned, repeated bedside examination after the acute phase is the best-supported safeguard, and it lists the design features that future studies would need.

Keywords: Organophosphate poisoning; Intermediate syndrome; Neuromuscular weakness; Respiratory failure; Acetylcholinesterase; Oximes; Narrative review

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Article Class: Narrative Review

1. Introduction

Poisoning with organophosphorus pesticides is a medical emergency that most clinicians in high-income settings

rarely meet and many clinicians in rural Asia meet every week. Surveys of fatal pesticide self-poisoning put a large share of the world's deaths from self-harm in



agricultural regions, with organophosphorus compounds prominent among the products swallowed (1, 2). The pattern reflects access more than intent: where highly hazardous products sit in the household shed, an impulsive act can be lethal (3, 4). Occupational and accidental exposure add a quieter burden (5).

Most of the textbook attention goes to the acute cholinergic crisis, the sweating, salivation, small pupils, slow heart rate and bronchial secretions that follow inhibition of acetylcholinesterase (6, 7). Atropine, supportive care and in some places an oxime are given, and a patient who survives the first day is often assumed to be through the worst of it. The intermediate syndrome challenges that assumption. After the cholinergic features have receded, usually a day to four days after the poisoning, some patients develop weakness of the neck flexors, the proximal limb muscles, the muscles supplied by cranial nerves and the muscles of respiration (8, 9). Without ventilatory support the respiratory weakness can kill.

This article reviews what has been published about that syndrome. Its question is narrow: how is the intermediate syndrome recognised, what is thought to cause it, what is associated with it, and how securely do the treatments tested so far affect its course? The article is a narrative review of the published literature on the topic in general. It does not describe any individual patient, hospital or district, and it reports no local data and no new analysis. The aim is a fair account of what is known and what is merely repeated.

2. Literature Review

2.1 Chemistry and Mechanism of Toxicity

Organophosphorus insecticides are esters of phosphoric or thiophosphoric acid. Their shared mechanism is

phosphorylation of the serine at the active site of acetylcholinesterase, which leaves the enzyme unable to break down acetylcholine at cholinergic synapses (10, 11). Many agricultural products are applied as thions, which have to be converted in the liver to the oxon form before they inhibit the enzyme strongly, and this conversion helps to explain why symptoms can build slowly after ingestion (12, 13). Fat solubility matters as well. A highly lipophilic compound can be stored in adipose tissue and released over days, which prolongs exposure in a way the plasma concentration at admission does not predict (14, 15).

Once phosphorylated, the enzyme can sometimes be reactivated by an oxime, but the phosphorylated enzyme may also undergo a chemical change called ageing, after which it no longer responds. The rate of ageing depends on the compound, and the kinetics of reactivation depend on both the compound and the oxime (12, 16). This is a reminder that “organophosphate poisoning” is a family of different poisonings. What the label hides is large: dimethyl, diethyl and other structural classes behave differently, and so do their solvents and additives, which may contribute to toxicity in their own right (17, 18).

2.2 Burden and Exposure

Pesticide self-poisoning is concentrated in rural parts of Asia, the Pacific and some other regions, and it has been estimated to account for a substantial fraction of suicides worldwide (1, 2). Case fatality varies with the specific pesticide swallowed, and prospective cohorts show that some organophosphorus compounds are far more lethal than others (18). Regulation that removes the most dangerous products from sale has been followed by falls in suicide in several countries, although the evidence base is



observational (19, 20).

This epidemiology matters for the intermediate syndrome in two ways. It means that many cases arise in hospitals with a few ventilators, where recognising weakness early decides whether a bed is available (21). It also means that the compound is often unknown or unconfirmed on arrival, which weakens any attempt to link the syndrome to a specific product. It is also one reason reported frequencies differ so much from place to place.

2.3 The Acute Cholinergic Phase

The acute phase has been described many times. Muscarinic effects, nicotinic effects at the neuromuscular junction and ganglia, and central effects appear in varying combinations, and management rests on airway protection, atropine titrated to dry chest secretions, and decontamination (22, 23). Observers noted early that fasciculations and weakness can occur within this phase, which is why the later weakness was at first lumped with it (9, 24). The distinction is partly one of timing and partly one of pattern: weakness in the acute phase accompanies other cholinergic signs, whereas the later weakness appears when those signs are fading.

Respiratory failure is the usual cause of death in the first days and has more than one origin. Bronchorrhoea and bronchospasm, central respiratory depression and neuromuscular weakness can each be responsible, and in practice they overlap (21, 25). A clinician cannot assume that a patient whose secretions are dry will keep breathing unaided. Timing, in this field, is rarely a detail.

2.4 Naming the Intermediate Syndrome

Descriptions of a neurological picture distinct from the acute crisis and from the later polyneuropathy go back to the 1970s (9). In 1987 two clinicians described a

series of patients in Sri Lanka who developed weakness of proximal and neck muscles, cranial nerve palsies and respiratory difficulty roughly one to four days after the acute event, and they called it the intermediate syndrome because it fell between the crisis and the delayed neuropathy (8). A prospective study in Belgium soon afterwards documented a similar sequence and added electrophysiological detail (26).

Table 1 sets the three phases side by side. The names are simple, but real patients do not always follow the sequence, and the boundaries between phases blur whenever a patient is partly treated, re-exposed, or poisoned with a compound that lingers (6, 7).

Table 1. Neurological phases that follow organophosphate poisoning.

Phase	Usual timing	Dominant features
Acute cholinergic crisis	Minutes to hours	Muscarinic, nicotinic and central features (6, 7)
Intermediate syndrome	Roughly one to four days, after the crisis settles	Weakness of neck, proximal limbs, cranial muscles and breathing (8, 26)
Delayed polyneuropathy	Weeks after exposure	Distal sensory and motor axonopathy (27, 28)

Note: Qualitative summary of the descriptions in the cited reviews; timing varies with the compound, the dose and the treatment given.

2.5 Delayed Polyneuropathy and Other Late Effects

The third phase has a different biology. Organophosphate-induced delayed polyneuropathy follows inhibition and ageing of a different target, neuropathy target esterase, and it produces a distal axonal degeneration that appears one to several weeks after exposure (27, 28). Not every compound that inhibits acetylcholinesterase has this effect, and the



chemical class decides the risk. Sensory involvement can be prominent and is sometimes overlooked (29). Reviews of chronic and low-dose effects describe cognitive and psychiatric complaints, but the causal evidence in that area is much less secure than for the acute and delayed neuropathic syndromes (15, 30).

Separating the intermediate syndrome from this later neuropathy is mostly a matter of distribution and time. The intermediate pattern is proximal, involves the neck and breathing and recovers over days to weeks, while the delayed pattern is distal and slower (14, 31).

3. Materials and Methods

3.1 Scope and Question

The review asks one question in two parts. What does the literature say about how the intermediate syndrome after organophosphate poisoning is recognised and explained? And how firmly does it support the treatments and monitoring patterns that have been tried? The first part is clinical and mechanistic; the second is a question about the quality of trials and cohorts.

3.2 Literature Assembly

The review draws on peer-reviewed reports in four areas: the chemistry and pharmacology of organophosphorus compounds; clinical descriptions and cohorts of acute poisoning; trials and systematic reviews of oximes, atropine, magnesium and decontamination; and reviews of the late neurological syndromes. Sources were selected by the authors' judgement from the English-language literature available up to the year of this issue, and older descriptive work was kept where it defined a term. We did not run a formal systematic search and we do not claim one. This is a narrative synthesis, and what it gains in breadth it loses in reproducibility. Reviews of this

kind are more useful when they say where the evidence ends than when they smooth over the join.

3.3 Appraisal Framework

To judge how far a report can be trusted we used four plain questions. Was the syndrome defined in advance, and by what bedside criteria? Were patients examined at set times or only when symptoms drew attention (32, 33)? Was the compound identified, and was treatment recorded in enough detail to be compared (18, 34)? And was the study large enough that a null result would mean something? An explanation is only as good as the data used to test it. None of these questions is hard, but each is easy to skip.

4. Results

4.1 Clinical Picture and Timing

The clinical description has been stable for three decades. Typical findings are weakness of neck flexion, weakness of shoulder and hip girdle muscles, drooping eyelids and weak eye movements, facial weakness, difficulty with swallowing and speech, and reduced breathing effort, with relatively spared distal muscles and tendon reflexes that may be reduced or absent (8, 26). The onset is usually described as one to four days after the poisoning and often follows the clearing of cholinergic features, though earlier and later onsets have been reported.

The best prospective cohort treated the syndrome as a spectrum. By examining patients repeatedly, its authors found that milder degrees of weakness, including neck flexor weakness without respiratory failure, were more frequent than the textbook picture, and that a rigid yes-or-no label obscured them (32). A later prospective cohort from India examined incidence and predictors and likewise relied on structured assessment (33). These studies agree that careful repeated



examination finds more of the syndrome than ad hoc observation does. A definition that cannot be applied the same way twice cannot be counted reliably.

Figure 1 places the three phases on a common time axis. The widths and overlaps are meant only to show order and relative timing, not measured durations. Recovery of the intermediate syndrome is generally described as occurring over days to a few weeks, and most patients who are supported through the period of respiratory weakness regain their strength (14, 24).

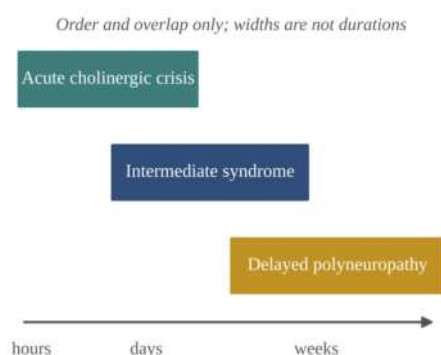


Figure 1. Timeline of the neurological phases after organophosphate poisoning (schematic, not data).

4.2 Proposed Mechanisms

Several explanations have been put forward, and Table 2 lists the main ones. The oldest links the syndrome to prolonged inhibition of acetylcholinesterase at the neuromuscular junction after exposure to highly lipophilic compounds, so that acetylcholine remains in the cleft for longer than the muscle can tolerate (8, 35). A related idea is that sustained stimulation alters the nicotinic receptor itself, through desensitisation or a changed number of receptors, so that transmission fails even once the enzyme has partly recovered (14, 35).

Two further proposals are about damage rather than function. Excess acetylcholine is known to injure muscle fibres in experimental settings, which could contribute to proximal weakness, and oxidative injury has been suggested as an

additional factor (15, 35). Finally, it has been argued that late or inadequate treatment, notably insufficient oxime early on, lets inhibited enzyme persist or age (12, 36). Figure 2 sketches how these routes might connect. They are not exclusive, and a single patient might have more than one at work. The proposals differ in what they predict, and few of those predictions have been put to the test.

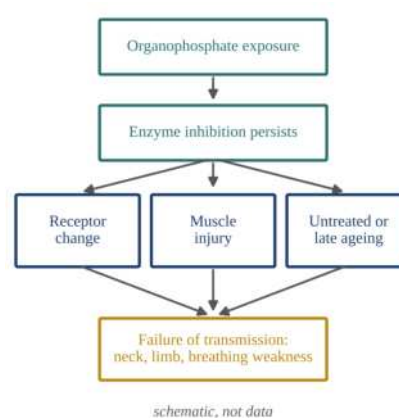


Figure 2. Routes proposed from enzyme inhibition to muscle weakness (schematic, not data).

Table 2. Proposed explanations for the intermediate syndrome.

Idea	Main argument	Main difficulty
Prolonged enzyme inhibition	Lipophilic compounds persist and keep acetylcholinesterase blocked (14, 35)	Enzyme activity does not map neatly onto weakness
Receptor change	Sustained acetylcholine alters nicotinic receptor function (8, 35)	Hard to show in living patients
Muscle injury	Excess acetylcholine damages muscle fibres (35)	Biopsy data are scarce
Inadequate treatment	Late or poor oxime and atropine therapy allows persistence (34, 36)	Trials disagree (37)

Note: None of these has been shown to be the sole cause; they are not mutually exclusive.

What is missing is direct evidence in living patients. Electrophysiological studies have



recorded abnormal responses to repetitive nerve stimulation in patients with the syndrome, which fits a problem at the junction, but they cannot tell us which of the mechanisms above is responsible (26, 32). The honest summary is that the syndrome is real, that the junction is the likely site, and that the cause remains open. A mechanism that is hard to measure is not thereby a mechanism that is absent.

4.3 Compounds and Risk Markers

Reports have linked the intermediate syndrome to a range of compounds, many of them lipophilic, and have suggested that the syndrome is more common after some products than others (32, 33). Because the compound is often unconfirmed at admission and patients may have taken mixtures with solvents, these associations are tentative (17, 18).

Severity of the initial poisoning, delay to treatment and the intensity of the acute phase have all been proposed as predictors, and the observational cohorts tend to find that more severe acute poisoning goes with more weakness later (21, 33). That is unsurprising, but it also means that severity is a confounder for any treatment effect: patients who receive more treatment are often sicker. Studies that do not account for this will tend to make the treatment look worse than it is. Adjusting for severity is therefore not a technicality.

4.4 Monitoring and Management

There is no specific treatment for the intermediate syndrome, and management is mainly supportive. The central task is to find respiratory weakness before it becomes failure, which is why repeated examination of neck flexion, proximal strength, cranial nerve function and breathing effort is stressed in clinical reviews (31, 38). Ventilatory support is given when breathing weakens, and most reviews advise ventilating early rather than

late, although the timing thresholds are based on experience and not on trials (21, 25). Table 3 summarises the main management questions and the support behind each.

Table 3. Management points in the intermediate phase and the strength of the support behind them.

Issue	Common approach	Evidence caveat
Surveillance	Repeated bedside tests of neck, limb and breathing strength (31, 32)	Observational support only
Ventilation	Early support when breathing weakens (21, 25)	Timing thresholds are not tested
Oximes	Used widely, dose and duration vary (36, 39)	Trials small and conflicting (34, 40)
Magnesium	Studied as an adjunct (41, 42)	Small trials, uncertain benefit
Decontamination	Removal of clothing and skin contamination, limited gut measures (38, 43)	Charcoal trial showed no clear survival gain (43)

Note: Descriptive only; no individual treatment advice is intended.

The oxime question remains unresolved. A systematic review of early trials found small studies with inconsistent results (39), and a later Cochrane review reached a similar conclusion about the weakness of the evidence (37). One trial of continuous pralidoxime infusion reported lower rates of the intermediate syndrome and death than repeated bolus doses (36), but it was small and single-centre. A randomised trial in Sri Lanka found no clear benefit from pralidoxime (34), and a pooled analysis raised the worry that oximes might even be



harmful, although the trials it combined differed greatly in design (40). Part of the discrepancy may lie in the compound, since the benefit of an oxime depends on how quickly the inhibited enzyme ages and how well the oxime reactivates it (12, 16).

Other measures have a thinner evidence base still. Magnesium sulfate has been studied as an adjunct, with small trials that suggest possible benefit but cannot settle the matter (41, 42). Multiple-dose activated charcoal did not improve survival in a large randomised trial of self-poisoning, which included organophosphate cases (43), and reviews of decontamination emphasise skin and clothing and the limited role of routine gut measures (22, 38). Atropine remains the mainstay of the acute phase, but it does not treat nicotinic weakness (6, 7). Figure 3 shows which features belong to which phase, and why the examiner's attention should shift from secretions to muscle strength as the days pass.

5. Discussion

5.1 Interpretation

Three things stand out. The first is that the clinical picture is consistent across decades and continents: proximal and neck weakness, cranial nerve involvement and respiratory failure after the cholinergic crisis. The second is that the explanation is far less secure than the description, and the several mechanisms in Table 2 are better seen as hypotheses awaiting a way to test them. The third is that the label itself has been used loosely. Where the syndrome is defined as respiratory failure, it will appear rarer than where it is defined as any neck flexor weakness, and the spectrum finding of the prospective cohorts suggests that the second definition is closer to the biology (32, 33). That is a modest conclusion, but it is the one the literature currently supports.

	Acute	Interm.	Delayed
Secretions, pupils	Shaded		
Neck, proximal weakness		Shaded	
Cranial nerve weakness		Shaded	
Breathing weakness	Shaded	Shaded	
Distal limb axonopathy			Shaded

Shaded = characteristic of the phase (schematic, not data)

Figure 3. Qualitative matrix of features by phase (schematic, not data).

For practice, the safest reading is that the period after the acute phase has its own risks and deserves its own plan. A patient who looks well on the second day may still need examination on the third and fourth, and the ward or intensive care unit should expect to look for weakness without waiting for the patient to complain (22, 31). This is not a claim about any individual patient, and it should not be read as individual advice.

5.2 Limitations

This is a narrative review, with the limits that follow. The sources reflect judgement, there was no formal search or quality scoring, and reports that found nothing may be under-represented. Much of the clinical literature consists of case series and single-centre cohorts, and the trials of treatment are small and use different regimens and definitions.

The review also leans on laboratory and mechanistic work to explain what clinical reports describe. Experimental findings in animals and in vitro are imperfect proxies for the human syndrome (10, 35).

5.3 Future Work

A study that could move the field would define the syndrome in advance with explicit bedside criteria, examine every patient at fixed intervals for several days,



identify the compound analytically instead of relying on history, and record oxime and atropine dosing precisely (32, 34). It would report the course of weakness in time, not just a yes-or-no outcome, and would adjust for the severity of the acute poisoning. Neurophysiological testing could be added to link clinical weakness to junction function (26, 35). Trials of treatment should consider stratifying by compound, since that may be where the benefit or lack of it arises (16, 18). Nothing here argues against treating poisoned patients actively; it argues for recording what happens when they are treated.

6. Conclusion

The intermediate syndrome is a well-described, sometimes fatal complication of organophosphate poisoning that appears after the acute crisis has seemingly passed. Its recognition rests on a stable pattern of proximal, neck, cranial and respiratory weakness, and the best-supported safeguard is planned, repeated examination so that ventilation is not delayed. Its cause is not established, and the effect of oximes and other treatments on its occurrence remains contested because the trials are small and the definitions inconsistent. Better studies, defined in advance and examined repeatedly, would resolve more than further case reports. Prevention at source, by removing the most hazardous products, remains the intervention with the clearest evidence of saving life (19, 20). It is a modest message, and a durable one.

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9. Conflict of Interest

The authors declare no conflict of interest.

10. Author Contributions

M.L. conceived the review and wrote the sections on clinical features and monitoring. S.G. wrote the sections on respiratory management and the evidence for treatment. H.H. wrote the sections on pesticide chemistry and exposure. All authors reviewed the literature, revised the manuscript and approved the final version.

11. Ethics Statement

This is a review of published literature. No patients were studied and no ethical approval was required.

12. Data Availability

No new data were generated. All sources are cited in the reference list.

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