Policy Analysis

SDMPH
SOCIETY FOR DISASTER MEDICINE & PUBLIC HEALTH

Pralidoxime Is No Longer Fit for Purpose as an Antidote to Organophosphate Poisoning in the United Kingdom

George Corby BA Medical Sciences [iD]

St John's College, University of Oxford, Oxford, UK

Abstract

Pralidoxime is the only oxime antidote to organophosphate poisoning stocked in the United Kingdom, produced by rational drug design in the 1950s. Typically, it is used alongside atropine, to reverse the effects of acetylcholinesterase inhibition. However, its efficacy has been questioned by recent meta-analyses of use treating attempted suicides in less economically developed countries, where organophosphate poisoning is more common. This policy analysis assesses the likely efficacy of pralidoxime in the United Kingdom, in scenarios largely different from those evaluated in meta-analyses. In all scenarios, the UK delay in antidote administration poses a major problem, as pralidoxime acts in a time-critical reactivation mechanism before "ageing" of acetylcholinesterase occurs. Additionally, changes in the organophosphates used today versus those pralidoxime was rationally designed to reverse, have reduced efficacy since the 1950s. Finally, the current dosage regimen may be insufficient. Therefore, one must re-evaluate our preparedness and approach to organophosphate poisoning in the United Kingdom.

Pralidoxime is the only oxime acetylcholinesterase (AChE) reactivator stocked in the United Kingdom, for use as an antidote to organophosphate poisoning, for use in combination with atropine.

Organophosphates were initially developed by the Schrader group in Nazi Germany as pesticides.[1] However, an accidental exposure resulted in Schrader being hospitalized for a fortnight,[2] leading to the realization that organophosphates had an alternative use as chemical weapons against humans, and before long, Germany had developed and stockpiled sarin and Soman organophosphates.[3] Resultantly, development of antidotes to this new class of chemical weapon began,[4,5] in an early example of rational drug design.[6] Oximes were shown to dephosphorylate organophosphate-inhibited AChE, with pralidoxime showing a favorable balance of high efficacy and low toxicity—leading to its use in humans by the mid-1950s—initially for patients exposed to pesticides.[7,8] Of particular importance, while antimuscarinics such as atropine block muscarinic receptors, only oximes such as pralidoxime directly reverse organophosphate inhibition of AChE—and so, theoretically, also have protective efficacy at both nicotinic and muscarinic receptors: protecting both the neuromuscular junction and parasympathetic autonomic nerve system.

Seventy years on from the rational design of pralidoxime, organophosphates have been used against civilians by the Iraqi[9] and Syrian[10] armies, twice in terrorist attacks in Japan,[11] and more recently, in the attempted assassinations of Sergei Skripal[12] and Alexei Navalny[13] in Europe. More impactfully, organophosphates are responsible for approximately 168,000 deaths per year: in 20% of suicides globally.[14]

Despite the clear ongoing impact of organophosphate use, meta-analyses have found no benefit, and potential harm, from use of pralidoxime in organophosphate poisoning for attempted suicides[15,16]; with a 2009 World Health Organization (WHO) report concluding that "The current body of evidence does not appear to support the continued use of pralidoxime for the treatment of organophosphate poisoning".[17] Nevertheless, the United Kingdom continues to stock pralidoxime as a therapy, alongside atropine, for organophosphate poisoning, despite this negative conclusion.

It is, therefore, necessary to assess the likely efficacy of pralidoxime in the United Kingdom, in substantially different contexts to the randomized controlled trials (RCTs) of pralidoxime use in attempted suicides in less economically developed countries.[15,16]

Therefore, one postulates and evaluates 3 scenarios that might occur in the United Kingdom, as illustrated on Figure 1: (1) accidental release of organophosphates from an industrial facility, (2) large scale terrorist/military attack, and (3) Skripal-like assassination attempts affecting few people.
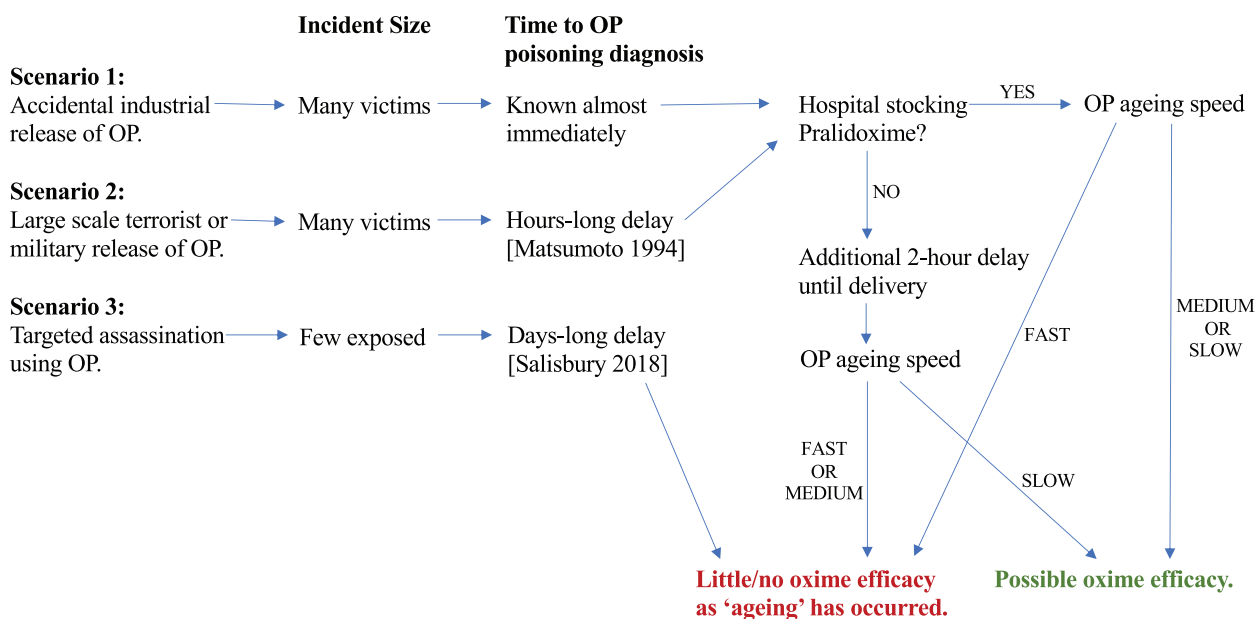
Figure 1. Outline of the response, and oxime efficacy following organophosphate (OP) exposure.

Discussion

Wrong Place, Wrong Time

Oximes work by reactivating an initial inhibited organophosphate-AChE adduct before an irreversible secondary "ageing" dealkylation reaction occurs. Critically, if pralidoxime is administered after AChE has "aged," it has zero "reactivating" efficacy.[17]

The ageing half-lives of organophosphates vary substantially: VR has an ageing half-life of 139 h, tabun 19 h, parathion-methyl 4 h, sarin 3 h, but soman just 6 min,[18] and cyanobacterial guanitoxin theoretically instantaneously.[19,20] Furthermore, the half-life of novichok agents (used in the Navalny and Skripal poisonings[13]) is not reliably published, but is believed to occur rapidly.[21] Therefore, unless pralidoxime is administered within minutes of Soman exposure, or hours of sarin exposure, it is unlikely to have any clinical benefit.

This poses a major problem for the United Kingdom, as pralidoxime is a "Category C" antitoxin—meaning it is held "supra-regionally". Indeed, approximately 2/3 of acute hospitals do not stock pralidoxime, and the mean estimated delivery time from holding centers to these hospitals was recently estimated to be 114 min.[22] Therefore, in scenario 1, there is a possible near-2-h delay until drug is administered to victims. In scenario 2—the nature of the chemical would be initially unknown, likely leading to a further delay in diagnosis of organophosphate exposure. This happened in Matsumoto 1994, where it took 3 d to diagnose sarin release by terrorists.[23] Alternatively, with few victims, scenario 3 may be even more challenging to identify—as organophosphate poisoning presents similarly to opioid overdose—which may be presumed first to the rare nature of organophosphate exposure.[13] Indeed, in the Skripal poisoning, pralidoxime was not administered until the following day.[13,24]

Therefore, as illustrated on Figure 1, in scenario 1, pralidoxime is likely to have no benefit for soman poisoning, but possible efficacy for medium/slow ageing organophosphates. In scenario 2, a day-long delay is likely to reduce the efficacy of pralidoxime to most organophosphates, whereas in scenario 3, only the

slowest-ageing organophosphates such as VR/VX will have reversal from pralidoxime administration.

Only with near instantaneous oxime administration can the fastest-ageing organophosphates such as soman be reversed. This was achieved through supply of 6.7m atropine-oxime auto-injectors to civilians in Israel during the Gulf War.[25] However, the much lower risk of organophosphate attack in the United Kingdom makes this economically unjustifiable here. Alternatively, whereas these delays might be inevitable for UK civilian use, in military contexts provision of auto-injectors, and a far higher index of suspicion of organophosphate exposure, may collectively enable faster recognition of attack, and administration of drugs—meaning these criticisms do not necessarily apply to military contexts.

One Size Does Not Fit All

Since the 1950s, it has been known that oximes may act particularly well (and better than pralidoxime) at reversing the poisoning of specific organophosphates.[26] Additionally, K-series agents have been shown to have efficacy against GA—which is impressive as GA has a lone amide electron pair—making nucleophilic attack impossible for pralidoxime.[27,28] More recently, research on donor blood has allowed direct comparison of particular organophosphates with specific oximes. For every single organophosphate tested, an oxime better than pralidoxime has been found—and obidoxime, which is widely used globally, was found to be at least 3× better than pralidoxime for most G- and V-series agents.[18] Further oximes are in development globally—although to date, pralidoxime, obidoxime, and trimedoxime have remained the key oximes licensed for use in humans.

In this context, even in scenarios 1 + 2, where pralidoxime might have efficacy, there likely exists an even better oxime—of which the UK stocks none for civilian use.

Ideally, multiple oximes would be stocked—and the best oxime for a specific organophosphate administered. Although there would inevitably be further delay in the context of time-critical

ageing, in the 1995 Tokyo attack, sarin was identified by gas chromatography/mass spectrometry within 2 h of the initial release[23]—so this is not impossible.

Too Weak, or Too Dangerous?

There is some indication that the WHO recommended dosage of pralidoxime may be too low.[17] The target plasma oxime concentration appears to be based off early experiments in cats,[17,29,30] which found anesthetized cats to be protected from organophosphates at this concentration—with further work showing this could be achieved in humans in 10 min with intramuscular injection of 20-30 µg/kg pralidoxime.[31] A fundamental problem with this extrapolation is that major differences in oxime efficacy exist between species,[32] making application to humans very difficult.

Subsequent analysis in humans indicates this may not be appropriate.

First, an RCT in 2009 compared the WHO regimen with placebo in patients with pesticide poisoning and found no reduction in mortality with pralidoxime use.[29] However, mortality was significantly lower in the patients where AChE activity successfully recovered—which may indicate that reactivating AChE does reduce mortality, but the WHO dosage is too low to have this effect in most patients. This is supported by a 2006 RCT, which compared high dose (above the WHO regimen) with low dose (below the WHO regimen) pralidoxime—with mortality 87% lower in the high dose group. Further research is needed, but there is, therefore, some indication that pralidoxime may work well as an oxime, but only at concentrations higher than currently recommended.

There is an alternative risk that pralidoxime might be harmful in some cases—with a nonsignificant harmful hazard ratio found in numerous meta-analyses.[15,16] Pralidoxime is toxic in excess, and early studies found that in rodents, pralidoxime has a minimum lethal dose of 100 µg/kg—at least 3× above that used in humans—causing death in 20 min through respiratory depression.[4] Although the mechanism is uncertain, as early as 1959,[33] and again more recently,[27] it has been shown that at high doses, oximes may paradoxically inhibit AChE. Additionally, there is some evidence that oximes are more toxic in patients exposed to carbamate pesticides (who may present clinically almost identically, as carbamates also inhibit AChE) rather than organophosphates, as oximes may augment inhibition of AChE in these scenarios.[34,35]

Conclusions

Organophosphates pose a major threat to human life, and have already been used for terrorist military means in the United Kingdom.[13] The need for an antidote to organophosphate poisoning is clear, but it is beyond doubt that there are major problems associated with the use of pralidoxime as an antidote to organophosphate poisoning in the United Kingdom.

Even in scenarios 1 and 2, where pralidoxime might be administered to patients within hours, pralidoxime may have little or no efficacy against the particular organophosphate the patient is exposed to, and be administered at a dosage too low to have clinically significant effect. In scenario 3, where longer delays highly probable, this is even more likely for all but the slowest-ageing organophosphates. In all cases, a superior oxime not currently stocked in the United Kingdom may exist—although substantial trial evidence of this is currently lacking. However, in this regard, even if alternative oximes were to be stockpiled for civilian use in the United Kingdom, without a change in the speed of drug distribution and administration, there may be no clinically significant benefit for patients, should organophosphate ageing be already complete.

These real-world hour-day long delays were never modeled in the original animal experiments used to design pralidoxime,[4,5,32,33] which may explain the lack of efficacy seen in modern trials.[15,16] Additionally, many novel organophosphates have been designed since the 1950s—meaning pralidoxime is used for organophosphates it was never designed to be used against.

Although higher-dosage regimens might prove to have better efficacy, this will raise drug costs—to around $400/patient in the case of the Pawar regimen,[36] which may be unacceptable given the exceptionally rare organophosphate poisoning incidence in the United Kingdom.

Therefore, pralidoxime is largely unfit for its purpose as an antidote to organophosphate poisoning in the United Kingdom, and the discussed chemical, systematic, and temporal deficiencies in current antidote therapy may result in additional deaths in future organophosphate poisonings.

References

1. **Nepovimova E, Kuca K.** Chemical warfare agent NOVICHOK - mini-review of available data. *Food Chem Toxicol.* 2018;121:343-350. doi: 10.1016/j.fct.2018.09.015
2. **Everts S.** The Nazi origins of deadly nerve gases. *Chem Eng News.* 2016;94(41):26-28.
3. **López-Muñoz F, Alamo C, Guerra JA, *et al.*** The development of neurotoxic agents as chemical weapons during the National Socialist period in Germany. *Rev Neurol.* 2008;47(2):99-106.
4. **Kewitz H, Nachmansohn D, Wilson IB.** A specific antidote against lethal alkyl phosphate intoxication. II. Antidotal properties. *Arch Biochem Biophys.* 1956;64(2):456-65.
5. **Childs AF, Davies DR, Green AL, *et al.*** The reactivation by oximes and hydroxamic acids of cholinesterase inhibited by organo-phosphorus compounds. *Br J Pharmacol Chemother.* 1955;10(4):462-465.
6. **Wilson IB, Ginsburg S.** Reactivation of acetylcholinesterase inhibited by alkylphosphates. *Arch Biochem Biophys.* 1955;54(2):569-571.
7. **Namba T, Hiraki K.** PAM (pyridine-2-aldoxime methiodide) therapy for alkyl-phosphate poisoning. *J Am Med Assoc.* 1958;166(15):1834-1839.
8. **Davies DR, Green AL.** The chemotherapy of poisoning by organophosphate anticholinesterases. *Br J Ind Med.* 1959;16(2):128-134.
9. **Balali-Mood M, Shariat M.** Treatment of organophosphate poisoning. Experience of nerve agents and acute pesticide poisoning on the effects of oximes. *J Physiol Paris.* 1998;92(5-6):375-378.
10. **John H, van der Schans MJ, Koller M, *et al.*** Fatal sarin poisoning in Syria 2013: forensic verification within an international laboratory network. *Forensic Toxicol.* 2018;36(1):61-71. doi: 10.1007/s11419-017-0376-7
11. **Yanagisawa N, Morita H, Nakajima T.** Sarin experiences in Japan: acute toxicity and long-term effects. *J Neurol Sci.* 2006;249(1):76-85.
12. **Khavrutskii IV, Wallqvist A.** β-Aminoalcohols as potential reactivators of aged Sarin-/Soman-Inhibited Acetylcholinesterase. *ChemistrySelect.* 2017; 2(5):1885-1890. doi: 10.1002/slct.201601828
13. **Eddleston M, Chowdhury FR.** Organophosphorus poisoning: the wet opioid toxidrome. *Lancet.* 2021;397(10270):175-177.
14. **Mew EJ, Padmanathan P, Konradsen F, *et al.*** The global burden of fatal self-poisoning with pesticides 2006-15: systematic review. *J Affect Disord.* 2017;219:93-104.
15. **Buckley NA, Eddleston M, Li Y, *et al.*** Oximes for acute organophosphate pesticide poisoning. *Cochrane Database Syst Rev.* 2011;(2):Cd005085. doi: 10.1002/14651858.CD005085.pub2

16. **Kharel H, Pokhrel NB, Ghimire R, et al.** The efficacy of pralidoxime in the treatment of organophosphate poisoning in humans: a systematic review and meta-analysis of randomized trials. *Cureus.* 2020;12(3):e7174. doi: 10.7759/cureus.7174

17. **Bevan M.** Proposal for the inclusion of pralidoxime in the WHO model list of essential medicines. In: Second meeting of the subcommittee of the expert committee on the selection and use of essential medicines. Geneva, 29 September to 3 October 2008.

18. **Worek F, Thiermann H, Szinicz L, et al.** Kinetic analysis of interactions between human acetylcholinesterase, structurally different organophosphorus compounds and oximes. *Biochem Pharmacol.* 2004;68(11): 2237-2248.

19. **Fiore MF, de Lima ST, Carmichael WW, et al.** Guanitoxin, re-naming a cyanobacterial organophosphate toxin. *Harmful Algae.* 2020;92:101737. doi: 10.1016/j.hal.2019.101737

20. **Hyde EG, Carmichael WW.** Anatoxin-A(S), a naturally occurring organophosphate, is an irreversible active site-directed inhibitor of acetylcholinesterase (EC 3.1.1.7). *J Biochem Toxicol.* 1991;6(3):195-201.

21. **Jeong K, Choi J.** Theoretical study on the toxicity of 'Novichok' agent candidates. *R Soc Open Sci.* 2019;6(8):190414.

22. **Harnett JT, Vithlani S, Sobhdam S, et al.** National audit of antidote stocking in UK emergency departments. *Eur J Hosp Pharm.* 2021;28(4): 217-222.

23. **Organisation for the Prohibition of Chemical Weapons.** The Sarin Gas Attack in Japan and the Related Forensic Investigation. 2001. Accessed January 31, 2024. https://www.opcw.org/media-centre/news/2001/06/sarin-gas-attack-japan-and-related-forensic-investigation

24. **Hulse EJ, Haslam JD, Emmett SR, et al.** Organophosphorus nerve agent poisoning: managing the poisoned patient. *Br J Anaesth.* 2019;123(4): 457-463.

25. **Bentur Y, Layish I, Krivoy A, et al.** Civilian adult self injections of Atropine – Trimedoxime (TMB4) auto-injectors. *Clin Toxicol (Phila).* 2006;44(3):301-306.

26. **Kozer E, Mordel A, Haim SB, et al.** Pediatric poisoning from trimedoxime (TMB4) and atropine automatic injectors. *J Pediatr.* 2005;146(1):41-44.

27. **Kuca K, Cabal J, Musilek K, et al.** Effective bisquaternary reactivators of tabun-inhibited AChE. *J Appl Toxicol.* 2005;25(6):491-495.

28. **Kassa J, Jun D, Karasova J, et al.** A comparison of reactivating efficacy of newly developed oximes (K074, K075) and currently available oximes (obidoxime, HI-6) in soman, cyclosarin and tabun-poisoned rats. *Chem Biol Interact.* 2008;175(1-3):425-427.

29. **Eddleston M, Eyer P, Worek F, et al.** Pralidoxime in acute organophosphorus insecticide poisoning—a randomised controlled trial. *PLoS Med.* 2009;6(6):e1000104. doi: 10.1371/journal.pmed.1000104

30. **Sundwall A.** Minimum concentrations of N-methylpyridinium-2-aldoxime methane sulphonate (P2S) which reverse neuromuscular block. *Biochem Pharmacol.* 1961;8:413-417.

31. **Sundwall A.** Plasma concentration curves of n-methylpyridinlum-2-aldoxime methane sulphonate (P2S) after intravenous, intramuscular and oral administration in man. *Biochem Pharmacol.* 1960;5(3):225-230.

32. **Davies DR, Green AL, Willey GL.** 2-Hydroxyiminomethyl-N-methylpyridinium methanesulphonate and atropine in the treatment of severe organophosphate poisoning. *Br J Pharmacol Chemother.* 1959;14(1):5-8.

33. **Berry WK, Davies DR, Green AL.** Oximes of alpha omega-diquaternary alkane salts as antidotes to organophosphate anticholinesterases. *Br J Pharmacol Chemother.* 1959;14(2):186-191.

34. **Faff J, Bak W.** Increase in sensitivity to obidoxime induced by fluostigmine in the rat. *Toxicol Appl Pharmacol.* 1978;46(2):429-433.

35. **Wille T, Kaltenbach L, Thiermann H, et al.** Investigation of kinetic interactions between approved oximes and human acetylcholinesterase inhibited by pesticide carbamates. *Chem Biol Interact.* 2013;206(3):569-572. doi: 10.1016/j.cbi.2013.08.004

36. **Pawar KS, Bhoite RR, Pillay CP, et al.** Continuous pralidoxime infusion versus repeated bolus injection to treat organophosphorus pesticide poisoning: a randomised controlled trial. *Lancet.* 2006;368(9553): 2136-2141.