

Letter from the editor

High dose pralidoxime in acute organophosphorus pesticide poisoning

Context: Organophosphorus poisoning, caused by deliberate self harm or occupational exposure, causes about 200 000 deaths each year worldwide, with case mortality rates reaching up to 20%. [1] [2] Organophosphorus pesticides inhibit acetylcholinesterase, resulting in an acute cholinergic crisis with malfunction of nerves and muscles, bronchospasm, seizures, and coma. Respiratory failure can occur acutely, or can develop many hours later, even after apparent recovery.[3] Standard treatments recommended by the World Health Organization (WHO)[4] include intravenous atropine and bolus doses of oximes (such as pralidoxime), which reactivate acetylcholinesterases.[5][6] However, there is only limited evidence that oximes reduce mortality after acute poisoning, and cost restricts their availability in developing countries. A recent study [7], carried out by Kirti Pawar and colleagues in India (where the incidence of organophosphorus poisoning is high), has investigated the benefits of high dose pralidoxime in acute organophosphorus poisoning.

Summary: Pawar and colleagues identified 200 people with moderately severe organophosphorus poisoning presenting within 24 hours of ingestion, who received intensive care support. [7] All participants received a bolus dose of 2 g pralidoxime plus a continuous intravenous infusion of atropine. Participants were then randomised to receive either a continuous infusion of high dose pralidoxime (1 g per hour for 48 hours), or a lower dose regimen similar to that recommended by the WHO (a bolus of 1 g pralidoxime every 4 hours for 48 hours). All patients who still needed to be ventilated after this time received a further 1 g bolus every 4 hours.

Findings: The people receiving the high dose infusion of pralidoxime were significantly less likely to require intubation, required a significantly shorter duration of ventilation, and received a lower median dose of atropine compared with those who received standard treatment (the investigators' primary outcomes, see table). Rates of death and pneumonia (the investigators' secondary outcomes) were also significantly lower in the high dose pralidoxime group. No substantial adverse effects were noted in either group and there were no delayed adverse effects or neurological complications in survivors at 52 weeks' follow up. A post hoc subgroup analysis showed similar response rates in people who had ingested diethyl organophosphorus compounds compared with those who had taken dimethyl compounds, contradicting prior belief that dimethyl compounds are less likely to be antagonised by oximes.

Outcome	Control group N = 100	High dose infusion group N = 100	Difference/Relative risk (95% CI)	P value
Requiring intubation	88/100	64/100	RR 0.72 (0.62 to 0.86)	0.0001
Median atropine dose in first 24 hours [mg; (95% CI)]	30 (25 to 45)	6 (4 to 6)	Difference: 24 (24 to 26)	>0.0001
Deaths	8/100	1/100	Adjusted for baseline variation: RR 0.11 (0.01 to 0.84)	0.0035
Pneumonia	35/100	8/100	Adjusted for baseline variation: RR 0.23 (0.10 to 0.47)	<0.0001

Appraisal: In a field characterised by scarce, poor quality evidence, Pawar and colleagues' study is a crucial and long awaited addition. However, the study presents some methodological issues of interest.

- At the start of the study, it was still unclear whether pralidoxime was beneficial in people with organophosphorus poisoning – there was a state of clinical equipoise with respect to treatment alternatives. In life threatening conditions, or where treatment is known to be beneficial, it is generally considered unethical to deny patients such treatment by allocating them to a placebo group. Yet, all too often, studies without placebo controls fail to show much difference between active treatments, and readers are left not knowing whether the treatments under investigation are both equally effective, or equally ineffective. In this study, the highly significant difference between the two active regimens means that we can be reasonably confident that high dose pralidoxime is beneficial compared with the standard regimen in the population investigated, even though we still don't know for certain whether the standard regimen, similar to that recommended by the WHO, is more effective than placebo.
- Several factors in the study design could have introduced bias: medical staff were not blinded to treatment allocation; the organophosphorus compound and dose ingested were not verified by toxicology tests, but based on the histories from the patients and their families; and severely ill patients were excluded from the study. There were also significant differences between the two groups in the type of organophosphorus compound ingested, and in the mean blood pressure, Glasgow Coma Scale scores, and butyrylcholinesterase levels on admission. However, the study outcomes remained significantly different even after adjustment for these baseline differences.
- The primary outcomes included requirements for supportive care, such as the need for, and duration of, ventilation. Although these are no doubt important outcomes for the hospital, the study's secondary outcomes of death and pneumonia are likely to be at least as important to patients. Demoting death and pneumonia to secondary outcomes risked the study being underpowered to detect clinically important differences in such key results. However, the benefits from the high dose regimen were so marked that a benefit was clearly demonstrated for these secondary outcomes.

Summary: The benefits from high dose pralidoxime infusions in acute organophosphorus poisoning in the study by Pawar and colleagues were of sufficient magnitude to overcome the methodological concerns about the study design. We agree with other commentators [8] that further research into the best treatment regimen for acute organophosphorus poisoning should still be supported, and that ways must be found to make such life saving but expensive treatments available in resource-poor countries, where they are most needed. Kirti Pawar and her colleagues are to be congratulated for undertaking this trial with such limited resources, for succeeding in publishing it in a way which will allow their results to be disseminated around the world, and for helping to save the lives of the many people affected by organophosphorus poisoning.

Alison Martin

Clinical Editor, *BMJ Clinical Evidence*

amartin@bmjgroup.com

Charles Young

Editor, *BMJ Clinical Evidence*

charles.young@bmjgroup.com

Conflict of interest: CY was previously an executive editor at The Lancet, and managed the submission of the Pawar paper to that journal. AM declares that she has no conflict of interest.

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