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EDITORIAL

Are Oximes Still Indicated for Acute Organophosphorus Insecticide Self-Poisoning?

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During the 1970s and 80s, organophosphorus (OP) insecticide self-poisoning became commonplace in rural Asia following their introduction into small-scale agricultural communities lacking the resources to use and store them safely [1]. Suicide rates increased exponentially as many acts of self-poisoning, previously non-lethal, became lethal due to the widespread availability of these highly toxic compounds (see the example of Sri Lanka [2, 3]). Fortunately, with effective pesticide regulation [4] and migration from rural agricultural communities to cities [5], the number of pesticide suicides has fallen from its 1990s peak. However, each year, an estimated 150,000 people still die from pesticide self-poisoning, with perhaps 100,000 deaths from OP insecticides [6].

When Tatusji Namba first reported the therapeutic use of the acetylcholinesterase (AChE) reactivator pralidoxime for occupational parathion poisoning [7], its clinical effectiveness seemed clear. A dose of 1 g produced rapid red cell AChE reactivation and clinical improvement and was recommended as routine therapy [8]. However, subsequent experience suggested that pralidoxime was less effective for certain OP insecticides, such as malathion, and following oral ingestion for self-harm. [9, 10]

This impression fitted with the poor clinical experience of pralidoxime in Asian hospitals treating patients with OP self-poisoning [11], in which a lack of pralidoxime was not apparently associated with worse outcome [12]. The clinical toxicology community's response to this lack of effect was that too low a dose was being used [13, 14]. Indeed, Namba himself recommended higher doses, including infusions of up to 0.5 g/h, in severe poisoning [10]. However, at the time of these recommendations, no clinical trials had been done to test the effectiveness of the higher doses.

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In this issue of *JMT*, Blumenberg and colleagues have carefully updated previous systematic reviews of clinical trials testing pralidoxime vs placebo, in addition to atropine and supportive care [15]. They have added two recent trials, one of which tested a high-dose regimen of pralidoxime (30 mg/kg loading dose then 8 mg/kg/h infusion for up to 7 days). They found no evidence for benefit from the addition of pralidoxime for outcomes of mortality or ventilation. This conclusion is also true when only patients receiving the high-dose regimen are included (3 trials, 181 pralidoxime vs 175 placebo patients). The WHO's conclusion that pralidoxime should not be an essential drug because we do not know which patients benefit from it [16] still stands.

Studies performed by the Munich group of Eyer and colleagues go some way to explaining this lack of effect [17, 18]. Acetylcholinesterase (AChE) inhibited by dimethyl OP insecticides, such as methyl-parathion and dimethoate, ages quickly, becoming unresponsive to oximes after only a few hours. Degradation of insecticides in the bottle, during storage and before use, as occurs with formation of isodimethoate or isomalathion, can increase toxicity and reduce even further responsiveness to oximes [19, 20]. S-alkyl OP insecticides such as profenofos do not appear to respond at all. [21]

Pralidoxime itself is a less potent AChE reactivator than oximes such as obidoxime [22]. This is important for the poisoning caused by WHO Toxicity Class II OP insecticides (such as dimethoate), which is globally now more common than poisoning with Class I OP insecticides such as parathion. Much larger quantities of Class II pesticides must be ingested for severe toxicity to develop due to differences in inherent toxicity (rat oral LD50 parathion 13 mg/kg vs dimethoate 150 mg/kg) [23]. Higher concentrations of pralidoxime are required to counter these doses of insecticide, increasing the risks of adverse effects [24]. When larger amounts of pesticide are ingested, the role of solvents and surfactants in the bottle become more important, raising the possibility of substantial non-OP toxicity resistant to AChE reactivation [25].

Overall, there are many reasons why oximes, especially pralidoxime, may not be effective for OP insecticide poisoning. But AChE reactivation should benefit some patients, when oximes are given at the right dose and at an appropriate time. Multiple phase II studies are now required, testing a variety of oximes against specific identified OP insecticides, using clinical and neurophysiological outcomes, before an appropriate large phase III RCT can be designed to test how we should use these drugs.

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