Editorial

Progress with reducing mortality from organophosphorus insecticide poisoning

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Keywords: Organophosphorus; Insecticide poisoning

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Cite this article as: Eddleston M. Progress with reducing mortality from organophosphorus insecticide poisoning. *Anuradhapura Medical Journal* 2014; **8**(1):1-4.
DOI: http://dx.doi.org/10.4038/amj.v8i1.6751

Twenty years ago, the medical and intensive care wards of Anuradhapura General Hospital were filled with patients severely poisoned by agricultural pesticides, particularly organophosphorus (OP) insecticides (1). After bans of parathion and methyl-parathion in the 1980s, (2,3) the most popular pesticides in agriculture and self-harm were the still highly toxic WHO Class IB (4) insecticides methamidophos ('Tamaron') and monocrotophos (2). These pesticides killed people quickly, from acute respiratory arrest and, perhaps after monocrotophos, from distributive cardiovascular shock. Many patients died in the community, before they were able to reach medical care (2).

The Registrar of Pesticides of the Department of Agriculture acted to reduce the import of all Class I pesticides, including methamidophos and monocrotophos, by 25% each year from 1992 until a complete ban came into force in 1995.(2, 3) This was the first such ban worldwide. Deaths from OP insecticide poisoning in Anuradhapura wards fell markedly but were unfortunately soon replaced by cases of severe endosulfan poisoning. This less inherently toxic insecticide - a WHO Class II toxicity organochlorine - was however very hard to treat and deaths due to status epilepticus became common. So this pesticide too was banned across the Island by the Registrar of Pesticides in 1998 and case numbers quickly faded away (2).

Ten years ago, the most important causes of pesticide poisoning in the Anuradhapura medical wards were the relatively less toxic WHO Class II OP insecticides, chlorpyrifos, dimethoate, and fenthion (5). These pesticides were about ten-fold less potent (in rat studies) than the older Class I OPs and patients now survived to secondary hospitals admission. But dimethoate was particularly severe, killing many patients from cardiovascular shock unresponsive to very large doses of atropine and adrenaline 12 to 48 hrs post-ingestion (5,6). However, despite an apparently large numbers of deaths in the Anuradhapura medical wards, there were now many fewer deaths in the community and far fewer deaths overall (7). Between 1995 and 2005, the overall suicide rate in Sri Lanka fell by 50% - due almost completely to a marked fall in the case fatality from pesticide poisoning (7).

Then these Class II OP insecticides were banned, along with two herbicides that were commonly lethal in overdose: paraquat and propanil. Over the last two to three years, there have been far fewer seriously ill pesticide-poisoned patients admitted to Teaching Hospital Anuradhapura than ever before. The case fatality for pesticide poisoning has fallen from around 14% in 2002 to just a few percent currently. The majority of this change is almost certainly due to the bans instigated by the Registrar of Pesticides. However, some of the reduction has come from better treatment of OP insecticide poisoned patients.

The two key antidotes for OP insecticide poisoning have not changed in 60 years. Atropine was first used in the USA during the 1950s; (8) it is still the primary antidote for OP poisoning (9). However, the collaborative clinical work performed in Anuradhapura and Polonnaruwa General Hospital medical wards in 2002-3 showed how poor the then international guidelines for atropine dosing were - sometimes recommending regimens that might take over 12 hours to give adequate atropine, leaving patients dangerously unstable (10). A protocol was developed (11) that was tested in an RCT in Bangladesh - this showed a

marked reduction in time to stabilisation and a remarkable drop in mortality from 22.5 to 8% (12). A recent review has shown how the North Central Province (NCP) work has been globally adopted (13).

The other antidote - pralidoxime (or the related obidoxime) (14) - is less unanimously appreciated. Developed in the USA in the 1950s,(15, 16) Janaka de Silva and Nimal Senanayake reported in 1992 that a shortage of pralidoxime in Peradeniya had no apparent effect on outcome (17). WHO International Programme on Chemical Safety (IPCS)-affiliated toxicologists responded that the dose being used in Sri Lanka was too low (9, 18). Yet, it reality, there was almost no high quality evidence for clinical benefit from oximes, especially after self-poisoning with WHO Class IB and II toxicity OP insecticides (19). In 2004, an RCT was set up in Anuradhapura and Polonnaruwa to test the high dose pralidoxime chloride regimen recommended by the WHO IPCS group. Unfortunately, no evidence of benefit was found; in particular, in addition to offering no obvious mortality benefit, it did not reduce the need for intubation or shorten the duration of ventilation (20).

This finding was in marked contrast to that of Kirti Pawar and colleagues in Maharashtra who published a RCT in 2006 of 200 patients with moderate severity poisoning;(21) this study found that a high dose of pralidoxime iodide was better than a lower dose for all outcomes, including death. This difference is surprising and might be due to patient selection in India and also the high-level intensive care that was offered to nearly all patients - 66% of the Indian patients were intubated at baseline compared to 17% in NCP, despite being less unwell. The current role for oximes in OP insecticide poisoning is unclear ;(22,23) further studies are required to determine whether benefit can be established using neurophysiological assays to identify patients responding and to identify better dosing regimens.

In the meantime, are there other possible treatments that could be simply and rapidly introduced into clinical practice?(24, 25) One such treatment might be nebulised salbutamol.

Although atropine is effective at stopping production of bronchial fluid during the cholinergic crisis, it does not increase its removal from alveoli. The tap is turned off but no effort is made to remove fluid from the lungs. A treatment that increases removal, to complement atropine-induced cessation of production, should speed the return of effective oxygen exchange and speed resuscitation. A single nebulised dose of the beta-adrenergic agonist salbutamol may do this since it increases alveolar fluid removal via the epithelial sodium channel (26). Nebulised salbutamol is available in rural hospitals worldwide and could easily be given alongside oxygen and atropine during initial resuscitation.

OP-induced neuromuscular junction (NMJ) dysfunction causes patients to require ventilation for several weeks, leaving them at high risk of death from complications. Its pathophysiology is uncertain; however, since it occurs despite effective muscarinic blockade with atropine, it is thought to be due to overstimulation of synaptic NMJ nicotinic receptors by excess acetylcholine, their subsequent down regulation, and neurotransmission failure (27, 28). No specific treatment exists.

We have recently established a minipig model of OP-induced NMJ dysfunction (29) and tested whether nicotinic antagonism is protective. Preliminary studies have shown that the neuromuscular blocker rocuronium protects the NMJ: removal with its antidote resulted in complete recovery of function. This suggests that administration of a neuromuscular blocker in patients requiring early ventilation may prevent nicotinic overstimulation and NMJ dysfunction, shortening the duration of ventilation and preventing complications.

Both salbutamol and a neuromuscular blocker, such as rocuronium or vecuronium, could now be tested in small RCTs to assess for any evidence of benefit. Such evidence should trigger dose finding studies and then formal Phase II/III RCTs to determine their cost-effectiveness in OP insecticide poisoned patients. These studies could be performed in NCP; however, due to the reduction of cases following the highly effective agricultural and public health interventions, these studies should also include other clinical centres in Asia where OP pesticide poisoning remains a major problem.

It may also be possible to work outside the medical and intensive care wards of Anuradhapura and Polonnaruwa, to improve clinical care of patients before they reach the main hospitals. Many patients become symptomatic before presenting to hospital. For some, respiratory arrest occurs and death ensues before intubation is possible; others present to a rural hospital with severe cholinergic features and die before onward transfer. An intervention that stabilised patients in the first hour after poisoning has the potential to save many lives.

Atropine auto-injectors are used widely by military and by adult and paediatric populations at risk of OP nerve agent exposure and have an excellent safety profile (30). Administration of atropine early in the community, via an auto-injector, to stabilise patients during transfer to hospital might save many lives. Community level studies will be required to determine whether people might accept this intervention and where the auto-injectors could be stored in the village to allow easy access.

Interventions might also work in rural hospitals, to improve the safety of patient transfers to Anuradhapura and Polonnaruwa. Poisoned patients often lose consciousness and aspirate gastric contents (31). Ideally, unconscious patients should be intubated before transfer. However, doctors in the smaller rural hospitals are often junior and intubate rarely, resulting sometimes in delayed and sub-optimal intubation due to infrequent practice. An intervention to safeguard an unconscious patient's airway that did not require intubation - such as a supraglottic airway (SGA)(32) - could markedly reduce the risk of aspiration and complications associated with inexperienced intubation. It would benefit those poisoned by any pesticide, with or without alcohol intoxication, reduce delays in transfer, and strengthen the system for

transfer of all unconscious patients. Both these pre-secondary hospital interventions could be tested in a factorial community cluster RCT.

Clinical trials in Sri Lanka, and particularly in Anuradhapura and Polonnaruwa, have guided worldwide clinical practice in pesticide poisoning over the last 10-20 years. Future clinical trials could continue to shape global clinical practice. At the same time, adoption of Sri Lanka's successful pesticide registration processes across rural Asia should markedly reduce global suicide.

Acknowledgements

ME is a Scottish Senior Clinical Fellow and Lister Prize Fellow; much of the clinical trial work performed in NCP was supported by the Wellcome Trust. ME thanks the academic, medical, and nursing staff of the Province for their collaboration and support in performing these studies, and for the patients for agreeing to enter trials. He also thanks his many Sri Lankan and international collaborators for their support.

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