Applied clinical pharmacology and public health in rural Asia – preventing deaths from organophosphorus pesticide and yellow oleander poisoning

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Self-poisoning with pesticides or plants is a major clinical problem in rural Asia, killing several hundred thousand people every year. Over the last 17 years, our clinical toxicology and pharmacology group has carried out clinical studies in the North Central Province of Sri Lanka to improve treatment and reduce deaths. Studies have looked at the effectiveness of anti-digoxin Fab in cardiac glycoside plant poisoning, multiple dose activated charcoal in all poisoning, and pralidoxime in moderate toxicity organophosphorus insecticide poisoning. More recently, using a Haddon matrix as a guide, we have started conducting public health and animal studies to find strategies that may work outside of the hospital. Based on the 2009 GSK Research in Clinical Pharmacology prize lecture, this review shows the evolution of the group's research from a clinical pharmacology approach to one that studies possible interventions at multiple levels, including the patient, the community and government legislation.

Introduction

Across the world, over 850 000 people die each year from self-harm [1, 2]. Two-thirds of these deaths occur in Asia where poisoning, and to a lesser degree hanging, are the main causes of suicidal death [3–5]. Pesticide self-poisoning kills at least 250 000 to 370 000 people each year [6], while plant or medicine self-poisoning is responsible for several thousand more deaths [7]. The problem is particularly severe in rural areas where pesticides and plants are widely available [8, 9]. Here the intensive care units of district hospitals are often filled with patients with pesticide-induced respiratory failure or aspiration pneumonia [9, 10].

The importance of pesticide self-poisoning for global suicide was recognized by the World Health Organization (WHO) in 2006 when it stated that pesticide poisoning was the single most important global means of suicide [11, 12]. A global campaign was then established with the aim of reducing deaths by increasing knowledge of its epidemiology, improving treatment and health care worker training, and improving dissemination of guidance [13]. Plant self-poisoning is a more local problem and has not received such international attention [14].

The involvement of clinical pharmacologists in managing poisoning seems obvious to those of us within the speciality, but is uncommon internationally. There are

enormous opportunities for clinical pharmacologists in this area, as this body of work shows.

Initial experience of poisoning in Asian medical wards

My interest in poisoning dates back to 1995 when I first went to Sri Lanka as a medical student at the invitation of Professor David Warrell to help with a clinical trial of antivenom for Russell's viper (*Daboia russelii*) envenoming [15]. However, few envenomed patients were admitted to the wards during the 2 months we were in Anuradhapura and I therefore spent my time observing patients being admitted to the medical wards.

Three remarkable groups of patients stood out, those with organophosphorus (OP) insecticide-induced respiratory failure (Figure 1), those with refractory status epilepticus after self-poisoning with the organochlorine insecticide endosulfan [16] and those with cardiotoxicity from yellow oleander poisoning [17]. All were common dramatic presentations that were stressful for the junior doctors since there was little effective treatment. The former were given pralidoxime that did not reverse the respiratory failure, organochlorine-poisoned patients received the GABA_A agonists diazepam and phenobarbital but usually still required a general anaesthetic for seizure control, while patients with oleander poisoning could only be given atropine to reduce vagal tone and then were transferred to the national hospital in Colombo for temporary cardiac pacing. Many of the pesticide and plant poisoned patients died despite these treatments.

Figure 1

An OP insecticide-poisoned patient being treated in Anuradhapura General Hospital after resuscitation and intubation. He is ventilated and has been administered atropine and pralidoxime. Insufficient intensive care capacity across rural Asia means that many such patients are managed on the open ward

An online review of the literature revealed that no research groups were active in researching these developing world poisonings and my interest in this subject took off.

Pharmacology of the common poisons

The most common poisons used for self-harm in much of South Asia are OP insecticides and seeds of the yellow oleander tree (*Cascabela thevetia* [L.] Lippold [18], heterotypic synonym *Thevetia peruviana*). Organochlorine insecticides were common but are now less important due to bans of their use in agriculture, often driven by their persistence in the environment [19].

OP insecticides inhibit the enzyme acetylcholinesterase (AChE) by phosphorylation of a serine in the active site [20]. They also inhibit multiple other esterases but the clinical significance of these effects is not clear [21]. AChE inhibition results in accumulation of acetylcholine and overstimulation of muscarinic and nicotinic receptors in synapses throughout the autonomic and central nervous systems and at neuromuscular junctions (NMJ). Patients present with classic muscarinic features (including bradycardia, hypotension, miosis, defaecation, urination, vomiting, coma, bronchorrhoea and bronchospasm) and nicotinic features (including sweating, fasciculation and sometimes tachycardia).

Most deaths occur from acute respiratory failure soon after ingestion (due to loss of central respiratory drive, neuromuscular dysfunction and direct effects on the lung) exacerbated by hypotension and bradycardia [22, 23]. In dimethoate poisoned patients, and possibly patients poisoned by some other OPs, early deaths also occur from severe distributive cardiovascular shock in ventilated patients [24]. Following hospital admission, further deaths occur due to complications of early loss of consciousness (aspiration, hypoxic brain injury) and to delayed neuromuscular dysfunction (termed the intermediate syndrome [25] or type II paralysis [26]).

Although OP insecticides predominate [7], many other pesticides are used in agriculture and are available for self-harm in rural Asia. Except for a few classes (such as carbamates, paraquat, aluminium phosphide, organochlorines, nitrite-based herbicides), the majority can be successfully treated with supportive care as long as the patient does not aspirate the pesticide. Most pesticides are formulated with a solvent (such as xylene) and a surfactant that can cause severe toxicity after aspiration.

Yellow oleander seeds contain a variety of cardiac glycosides including thevetoxin, thevetin A and B and neriifolin [27]. The glycosides inhibit the Na⁺/K⁺ ATPase that extrudes sodium and imports potassium into cardiomyocytes. Inhibition causes build-up of sodium, which increases intracellular calcium, which in turn induces

further calcium release from the sarcoplasmic reticulum [28]. The myocardium becomes irritable and arrhythmogenic. In addition, increased vagal tone causes bradycardia. Poisoning manifests with abdominal pain, vomiting, diarrhoea, hyperkalaemia and cardiac dysrhythmias (in particular atrioventricular [AV] block) [27]. Patients die from ventricular tachydysrhythmias usually resistant to defibrillation, sometimes triggered by pacing wires being inserted for severe bradycardia.

Clinical trial of anti-digoxin Fab in oleander poisoning

While in Sri Lanka in 1995, I learnt that the snake antivenom manufacturer was developing a Fab fragment antidote (now commercialized as DigiFab) that bound to cardiac glycosides to reverse their toxic effect. I was offered the chance to test it against yellow oleander poisoning and so took a year off clinical school to return to Sri Lanka. After 3 months working in Anuradhapura seeing oleander poisoned patients [17, 29], getting ethics approval and organizing the study, I started the clinical trial at the Coronary Care Unit in Colombo with my Sri Lankan colleagues Drs S. Rajapakse, K. Rajakanthan and S. Jayalath under the supervision of the unit's consultant cardiologists and my Sri Lankan mentor Professor M.H. Rezvi Sheriff.

Over 6 months, we recruited 16 patients to a small dose-finding study and then 66 patients to a randomized controlled trial (RCT) that tested 1200 mg of anti-digoxin Fab against placebo, in addition to standard therapy (atropine $\pm$ isoprenaline and temporary cardiac pacing). All had substantial cardiotoxicity. The study showed that the antidote was clearly effective at reversing cardiotoxicity [30]. The first thing we noticed was that patients' abdominal pain and vomiting settled within minutes of antidote administration and the dysrhythmias then settled over 1–2 h (Figure 2). There was a rapid increase in heart rate and 50% of dysrhythmias had completely resolved by 3 h, compared with 30 h in control patients. The study was small and did not look at mortality. However, oleander mortality results from cardiotoxicity. Therefore an antidote that resolves cardiotoxicity appeared likely to reduce deaths.

A prospective cohort of acute self-poisoning patients

I had to return to medical school and basic clinical training but was fortunate as a senior house officer to receive an intermediate fellowship from the Wellcome Trust with which to return to Sri Lanka. By this point, in addition to David Warrell, I had started to work with two researchers who mentored my clinical toxicology and research methodology: Nick Buckley from Adelaide and Ed Juszczak from Oxford. We together set up a cohort to record better the

Figure 2

Reversal of oleander-induced AV node block in a patient administered anti-digoxin Fab. The treatment was given at time zero. The baseline trace shows third degree block with a variable ventricular rate (the P waves overlie the T wave initially before separating away as the ventricular rate changes). At 30 min, the predominant rhythm is second degree AV block. By 60 min, the rhythm has converted to first degree AV block which has resolved by 2 h. On the x-axis, the ticks represent one small square on an ECG sheet or 200 ms; the figure shows just more than 6 s. Taken from reference [30]

natural history of pesticide and plant poisoning in resource poor locations. Into this cohort, we initially nested two clinical trials, one of activated charcoal and one of pralidoxime.

Ethics approval for these studies was received from the University of Colombo's Faculty of Medicine research ethics committee and the Oxfordshire Tropical Medicine ethics committee. Later studies also received ethics approval from the Sri Lanka Medical Association's ethics committee and from ethics committees in Australia.

Our first task was to integrate research practice into the medical wards of Anuradhapura and Polonnaruwa General Hospitals, the two major hospitals serving North Central Province. We chose to work in these hospitals because they received patients from over 50 small peripheral hospitals

across the province [31]. These hospitals transferred 50–75% of their poisoned patients, including practically all sick patients, after gastric decontamination [32]. As a result we were able to recruit several thousand patients each year to the cohort from just these two sites.

We also aimed to standardize initial patient care. When we arrived, such care consisted of mechanical forced emesis (with large volumes of water or sodium bicarbonate) or gastric lavage using a large bore orogastric tube [33]. The procedure was done before medical assessment and in unmonitored patients. Patients were unable to refuse and gastric lavage was done forcibly if necessary. The techniques were popular with staff and the community since they were thought to be life-saving, despite lacking evidence for benefit and being associated with clear harm to patients [33].

After much debate amongst medical and nursing staff, we were permitted not to lavage patients if they gave consent to being recruited to the charcoal RCT. Initially several ward staff were hostile to the study because we did not lavage. However, over time, hospital staff came to accept the study as it was able to show that careful resuscitation, observation and supportive care without gastric lavage appeared safe.

Observational studies

Observation of patients admitted with acute self-poisoning to the ward revealed clear differences in clinical syndrome and outcome after poisoning by OP insecticides with similar animal toxicity [24]. It allowed us to report the first prospective care series of poisoning with several herbicides [34, 35], test the cost-effectiveness of anti-digoxin Fab in clinical practice [36], and directly compare for the first time human toxicity of pesticides ingested for self-harm [37]. We were also able to work with Martin Wilks to study the effect of changing the formulation of the herbicide paraquat on human toxicity [38].

An RCT of multiple doses of activated charcoal

The first RCT aimed to test the effectiveness of multiple doses of activated charcoal in reducing deaths from self-poisoning. Activated charcoal binds to poisons in the stomach and reduces absorption if given early. At later times, it can increase poison elimination by interrupting the enterohepatic circulation and the diffusion of poisons between gut and blood (enterovascular circulation). The elimination of digitalis is increased by charcoal [39, 40]. We hypothesized that charcoal would also increase elimination of oleander cardiac glycosides and offer clinical benefit to patients presenting after some hours. Some pesticides also bind to charcoal *in vitro* [41]. Therefore we

recruited patients with practically all forms of poisoning into the study. To clarify whether it was multiple doses of charcoal rather than the first dose that offered any benefit, patients were allocated to one of three arms: no gut decontamination, a single 50 g dose of activated charcoal or an initial 50 g dose of activated charcoal followed by five further doses given at 4 h intervals. The primary outcome was mortality.

Over a little more than 2 years, in three hospitals, we recruited 4632 patients to the trial [42]. Over half (51%) of patients had ingested pesticides, whereas one third had ingested yellow oleander seeds. Charcoal did not alter the primary outcome: 97 (6.3%) of 1531 participants in the multiple dose group died compared with 105 (6.8%) of 1554 in the no charcoal group (adjusted odds ratio 0.96, 95% CI 0.70, 1.33, Figure 3). No significant effect was noted for patients who took particular poisons, were severely ill on admission, or who presented early [42].

Multiple-dose (and single dose) activated charcoal did increase the elimination of oleander cardiac glycosides, although to the same extent [43], and multiple doses did reduce the incidence of severe dysrhythmias that required patients transfer, but did not reduce deaths [42]. This result was quite different from that reported from an earlier trial of activated charcoal in oleander poisoning [28, 44]. The reason for this difference is unclear. This trial was smaller (with 401 patients) and had a high case fatality in the control arm that received a single dose of charcoal. A large proportion of deaths occurred in this arm from dysrhythmias after 24 h that could have been related to the high doses of atropine administered [45, 46]. A meta-analysis of the two studies indicated that combined evidence did not suggest a major effect of charcoal in oleander poisoning [45].

Pralidoxime for symptomatic OP insecticide poisoning

The second nested trial focused on OP insecticides. After resuscitation, standard therapy involves administration of oxygen and atropine to counter the effect of excess acetylcholine at muscarinic receptors [47, 48]. Atropine dries up secretions, improving pulmonary function and restores adequate cardiovascular function. However, it is not able to prevent acute respiratory failure that results from loss of central respiratory drive and neuromuscular junction dysfunction (which is probably due to nicotinic receptor overstimulation). Patients therefore require mechanical ventilation, sometimes for several weeks, leaving them at significant risk of complications of ventilation.

In the 1950s, the antidote pralidoxime was found to reactivate inhibited AChE, restoring normal cholinergic function [49]. It clearly appeared to benefit individuals with low dose occupational poisoning by highly potent OPs, such as parathion [50]. However, its efficacy for very high

†Test for trend

†Test for trend

Figure 3

Forest plot of mortality for A) multiple dose activated charcoal vs. no activated charcoal and B) single dose activated charcoal vs. no activated charcoal. *Test for trend. MDAC = multiple dose activated charcoal; AC = activated charcoal; OP = organophosphorus; GCS = Glasgow comma score. Taken from reference [42]

Figure 4

Forest plots of mortality for pralidoxime vs. placebo for *a priori* defined study groups. The relatively few events precluded adjusted analyses plots. Taken from reference [54]

dose intentional poisoning with common agricultural OPs, such as dimethoate, was not clear and the subject of much debate in Asia [51]. The WHO advised using higher doses for self-poisoning [52] but the evidence was lacking [53]. We therefore tested its effectiveness against poisoning with WHO Class II moderately toxic OP insecticides, such as chlorpyrifos and dimethoate.

We compared the WHO recommended regimen (pralidoxime chloride 2 g loading dose over 20 min, followed by 0.5 g h⁻¹ [48] for up to 7 days or until atropine was no longer required) against saline placebo, in addition to usual therapy. Blood samples were taken both before and after pralidoxime administration to assess its pharmacokinetics and pharmacodynamics, and confirm the OP identity in each patient. We planned to recruit 1500 patients. However, we had major problems starting this study due to hoarding of pralidoxime after the September 11 2001 attacks and then heat damage of study drug during its transport from Australia to Sri Lanka. It was only in 2004 that we were able to start recruiting patients. Unfortunately, the trial then stopped early in 2006 with just 235 patients recruited [54], after publication of a positive study from India [55] resulted in loss of equipoise among collaborating clinicians.

The subsequent results of our study analysis were surprising: we found no evidence of benefit from this regimen of pralidoxime in patients with WHO Class II toxicity OP poisoning. The PKPD studies showed that we gave the correct dose and that pralidoxime worked, in that it reactivated red cell AChE. However, mortality was non-significantly higher in patients receiving pralidoxime: 30/121 (24.8%) compared with 18/114 (15.8%) receiving placebo (adjusted hazard ratio [HR] 1.69, 95% confidence interval [CI] 0.88, 3.26, *P* = 0.12, Figure 4). Incorporating the baseline degree of AChE ageing and plasma OP concentration into the analysis increased the HR for patients receiving pralidoxime compared with placebo, further decreasing the likelihood that the drug is beneficial. The need for intubation was similar in both groups (pralidoxime 26/121 [21.5%], placebo 24/114 [21.1%], adjusted HR 1.27, 95% CI 0.71, 2.29).

There is a great deal of variation between OP insecticides [24]. Therefore, it is difficult to make direct comparisons between patient groups poisoned by a variety of OPs. To reduce this confounding, we analyzed patients with either confirmed chlorpyrifos or dimethoate poisoning only. This analysis also found no evidence of benefit despite chlorpyrifos being an OP that is highly sensitive to oxime-induced reactivation.

The reasons why we found no effect, and for the marked difference in results compared with the Indian study [55], are unclear. Rapid administration of pralidoxime can cause cardiorespiratory arrest [56]. Few of the patients in our RCT were intubated (17%) or in ICU at the time of pralidoxime administration while 66% of the Indian trial's patients were intubated and all were in an intensive care unit of a private hospital [55]. It is possible that better supportive care, as is not routinely available in the Asian

government hospitals that admit most OP poisoned patients, is required for pralidoxime to be given safely. In support of this hypothesis, the only patient group in our study without any evidence of harm from pralidoxime were those who were intubated at baseline (HR 0.95, 95% CI 0.43, 2.13) [54].

Following pre-publication reporting of our trial and independent synthesis of a systematic review, in 2009 the WHO decided not to place pralidoxime on their Essential Drugs List [57].

Complications of clinical trials

This work was not simple. In January 2003, I was accused of killing a patient at a third hospital at which we had started working. Initially announced on one of the national radio stations, the story was rapidly taken up by Sinhala language newspapers. The patient had been recruited to the charcoal RCT (consented by his family) after ingestion of a bottle of dimethoate insecticide and subsequently died. We subsequently found out that the problem was personal, with our study being attacked due to conflict between a hospital consultant and my colleagues. We were initially shut down in this third hospital. Only strong support from the medical and nursing staff in the two other study hospitals, in the face of strong outside calls for the study to be stopped, permitted the study to continue.

Unfortunately, the problem was then escalated to a national level and one day I was called by the Provincial Director of Health Services to be told that we had to stop on the instructions of the Secretary of Health, the chief medical civil servant. The next few months were very difficult. During them I received one piece of very valuable advice from an Oxford colleague, Francois Nosten – ‘you will only be able to start the trial again if the local people really want it to happen’. We were fortunate in that this decision was made locally. Four months after the initial incident, we were permitted to start again in the two hospitals that had wanted to continue the study and it ran smoothly thereafter.

Continuation of the cohort

Throughout 2002–2004, Nick Buckley visited the study hospitals to offer clinical and study advice. In 2003, we wrote a grant application to the Wellcome Trust and Australia’s National Health and Medical Research Council (NHMRC) to continue research and create a regional toxicology research centre. This was funded and in June 2004 Andrew Dawson moved to Peradeniya in the central highlands of Sri Lanka to direct this research and capacity building work. The grant created the South Asian Clinical Toxicology Research Collaboration (SACTRC) out of the original Oxford-Colombo collaboration.

The SACTRC cohort continued after I moved back to the UK and by the end of 2010, it had clinical and outcome data on over 30 000 patients. A series of small phase II clinical studies was done to pilot test a number of antidotes, such as clonidine for OP pesticide poisoning [58], fructose diphosphate (FDP) for oleander poisoning [59] and salicylate for paraquat poisoning, as well as a bigger phase III trial of immunosuppression in paraquat poisoning by Indika Gawarammana and colleagues.

Another major achievement of SACTRC has been in supporting Sri Lankans to obtain MPhils and PhDs. By Sept 2012, a total of 19 postgraduate degrees had been awarded for research projects under its auspices.

Co-ingestants and complementary animal work

Our RCT surprisingly showed that pralidoxime was poorly effective in OP insecticide poisoning. We wondered therefore whether co-ingestants might be important for toxicity, explaining why AChE reactivation was not beneficial.

We first looked at the role of alcohol, since many of the male patients who died had also ingested alcohol. As a CNS depressant like OP insecticides, alcohol might worsen toxicity. We analyzed plasma alcohol and OP concentrations and patient outcome in a series of patients poisoned by one OP, dimethoate [60]. We noted that patients who died had both higher alcohol and higher dimethoate plasma concentrations at admission. However, only plasma dimethoate was associated with outcome. We concluded that ingestion of alcohol increased the quantity of dimethoate ingested (due perhaps to loss of impulse control or of taste [the stuff tastes awful]) but did not affect the toxicity of the overdose itself. This was reassuring for our clinical management of patients.

We then looked at the role of coformulants. Agricultural insecticides are formulated with solvents and surfactants to increase their usability by farmers [61]. The pure insecticide, the ‘active ingredient’ (AI), is not by itself usable. To explore their role, we established a Gottingen minipig model of agricultural dimethoate poisoning, using the standard 40% emulsifiable concentrate formulation (dimethoate EC40) that is ingested by humans [62]. The preparation contains 40% dimethoate, 40% cyclohexanone, 5% xylene and a surfactant called Wettol (since the surfactant is considered non-toxic, the company does not declare its concentration in the preparation). We chose this model since pigs appear to be good toxicology models in general [63, 64] and specifically for human OP poisoning [65]. The pesticide was given by gavage and the pig treated with intensive care, as would happen for poisoned people.

We found that one of the solvents in dimethoate EC40, cyclohexanone, was fundamental for toxicity [66]. Dimethoate EC40 2.5 ml kg⁻¹ (containing 1.0 g kg⁻¹ dimethoate AI) caused severe toxicity, with early respiratory arrest and car-

diovascular collapse that could be transiently treated with very large doses of norepinephrine. The pattern of poisoning was very similar to that of human poisoning [62], including a complete lack of effect of pralidoxime [24]. A lower dose of dimethoate EC40 (1.25 ml kg⁻¹) produced only modest toxicity. Dimethoate AI alone similarly caused only modest toxicity easily treated with norepinephrine infusions, as did cyclohexanone alone. In contrast, the combination of dimethoate AI and cyclohexanone reproduced the toxicity of dimethoate EC40, indicating that the solvent was required for full toxicity [66]. A novel formulation of dimethoate EC, lacking the cyclohexanone, was less toxic in this model. The mechanism of this effect is not yet known. Future studies are required to determine whether reformulation of OP insecticides with safer solvents could reduce the number of suicides in rural Asia.

Respiratory failure

Acute respiratory arrest is the main cause of death in OP insecticide poisoning. Where highly toxic OPs, such as parathion and monocrotophos are used in agriculture, poisoning onset often occurs soon after ingestion so that respiratory failure happens before patients reach medical care. Patients die in the community or suffer from complications such as aspiration or hypoxic brain damage.

In Sri Lanka, the most highly toxic OPs are no longer used in agriculture and relatively few people die before hospital admission. Instead respiratory arrest tends to occur at least several hours post-ingestion when the patient has arrived in hospital. Unfortunately, mechanical ventilation is often not life-saving since ventilation may be required for several weeks, leaving patients at risk of pneumonia, lung injury and thromboses. A way of reducing the length of time a patient is ventilated could save many lives. We had hoped that pralidoxime would reduce the need for ventilation but were disappointed by the RCT's result.

The mechanism of respiratory failure is not completely clear. The early respiratory arrest during the acute cholinergic crisis is likely to be due predominantly to a central loss of respiratory drive and to local effects in the lungs (bronchorrhoea and bronchoconstriction), with a lesser degree of NMJ dysfunction. However, phrenic EMG studies have not been done during the acute stage to test this hypothesis – a reduction in impulses passing down the nerve would support the idea of a central cause.

After some hours to days, there is evidence of severe NMJ dysfunction that may result in respiratory failure lasting several weeks. It can come on early, during the cholinergic failure, or later after the cholinergic crisis has settled and the patient becomes conscious again. In the latter situation, it has been termed type II respiratory failure [26] or the intermediate syndrome [25]. It seems likely that this NMJ dysfunction is due to overstimulation of nicotinic receptors on pre-synaptic ($\alpha 3\beta 2$ receptors)

and/or post-synaptic (adult muscle type receptor) membranes, since muscarinic receptors are likely to be blocked with atropine given to patients to control muscarinic features.

Our minipig model developed NMJ dysfunction that was similar to the NMJ dysfunction of human patients. Pilot studies have shown that administration of a rocuronium infusion sufficient to inhibit NMJ function by about 99% before administration of dimethoate EC40 reduced NMJ damage at 6 h. Rocuronium is a competitive nicotinic antagonist that works on both pre- and post-synaptic receptors and may work by protecting these receptors from over-stimulation. If further pig studies confirm this finding, we will try to use this therapy for human poisoning. We hope that treating a poisoned patient with rocuronium for 2–3 days will prevent the damage that necessitates long term ventilation, reducing the risk of ventilator-associated complications.

Complementary public health research

Treating patient after patient in the hospital, with often modest success, soon made us realize that public health approaches were necessary to complement our clinical work. Following the work of Haddon [67,68], we developed a Haddon matrix to identify interventions that might reduce the case fatality following self-poisoning [69]. Using an industrial harm minimization approach, it was clear that legislative changes were the most likely to be effective [16].

David Gunnell, Ravindra Fernando and colleagues looked at how pesticide regulation during the 1980s and 1990s affected overall suicide rates [70]. Remarkably, they found that the bans stopped the exponential increase in suicide rate seen in the 1960s and 1970s after the Green Revolution pushed pesticides into many rural households. In particular, legislation passed in the 1990s that banned all of the most toxic (WHO Class I) OPs and the organochlorine, endosulfan, from agricultural practice resulted in a rapid halving of the nation's overall suicide rate. Over 10 years, an estimated 17 000 lives had been saved by legislative action. Of great interest, this rapid fall in pesticide suicides had not been countered by either major rises in other forms of suicide, such as hanging [70], or any rise in agricultural costs or a reduction in yields [71].

From around 2004, Flemming Konradsen had worked with Sri Lankan researchers to understand whether the provision of safe storage boxes to rural households might reduce pesticide poisoning. This seemed to him to be a very active form of intervention, unlikely to be sustained in the medium term [72], but was a popular option. Pilot studies carried out in four Sri Lankan villages showed that the boxes did result in household pesticides being locked away but also that the boxes caused pesticides to be

Figure 5

A) Location of the Safe Storage study in Sri Lanka and B) the lockable pesticide container being tested

brought into the house rather than stored in the field. Locking of storage containers dropped off over time. In addition, in the household, there was a risk of the boxes being broken into [72, 73].

To assess the cost-effectiveness of providing an 'in-field' storage box to rural households, we sought funding from the Wellcome Trust to set up a cluster RCT in 162 rural

Sri Lanka villages in the Mahaweli H region of Sri Lanka (Figure 5A) [74]. This was funded and at present over 28 000 households have been recruited and over 4 000 out-of-house storage containers (Figure 5B) distributed to households. This study will determine whether reducing availability of pesticides at times of stress will reduce the incidence of pesticide self-poisoning.

Impact

This series of studies has had some impact. Anti-digoxin Fab was introduced into Sri Lanka for about 1 year before funds dried up. During this time it saved an estimated 300 lives [36]. Pralidoxime was not added to the WHO's Essential Drugs List [57]. The WHO stated that pesticide poisoning was the single most important global means of suicide and set up a global prevention campaign based to a large extent on our work [11, 12]. A recent WHO document describing ways to prevent deaths from pesticide poisoning had six references in its summary section [75]. All six papers were from our group.

Conclusion

Over the last 10 years, we have set up the first large prospective cohort of self-poisoned patients in the developing world and developed an active collaboration of investigators from Sri Lanka, UK, Australia and Denmark. The group has researched the natural history and treatment of common, lethal forms of poisoning and nested

multiple clinical trials into the cohort (Table 1). At the same time, we have established a large animal model to perform pre-clinical studies that will directly affect human treatment. A complementary public health intervention study will test whether pesticides can be better stored in rural households, to reduce poisoning.

Some future work will be based on the animal work, moving us back into clinical trials and into public health interventions by attempting to alter pesticide formulation, for example. Further antidotes will be tested for pesticide and plant poisoning. A large cluster RCT may be possible to test the health and agricultural effects of banning all OP and carbamate pesticides and replacing them with more expensive but potent modern pesticides.

Competing Interests

The author has completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declares ME had support from the Wellcome Trust, Chief Scientist Office of Scotland and the Lister Institute for Preventative Medi-

Table 1

Preventing self-poisoning deaths using a risk minimization approach. Past and future research by the SACTRC group & collaborators

Level	Intervention option	Notes
Legislation	1.1 Legislation to ban highly toxic pesticides (mostly WHO Class I) from agricultural practice 1.2 Legislation to ban all OPs and carbamates from agricultural practice 1.3 Reduce hazardous alcohol consumption	Bans implemented during the 1990s produced a 50% reduction in overall suicides [70]. The bans had a neutral effect on agricultural costs and outputs [75]. Based on human toxicity data [37], a pilot study showed feasibility of banning OP insecticides [76]. Large cluster RCT under design to study agricultural and health effects of such a ban. Intoxicated people drink larger amounts of pesticide [60]. Reducing pre-event alcohol consumption may improve prognosis
Community	2.1 Provide lockable household containers for pesticide storage 2.2 Improve selling practice by pesticide shops to reduce sales to high risk individuals 2.3 Improve safety by reformulation 2.4 Change solvents in OP formulations to reduce human toxicity	Pilot studies have suggested that in-house storage may be hazardous [72, 77]. Large cluster RCT assessing cost-effectiveness of providing household storage containers [74]. Observational studies performed (Wickramasinghe, under review). Possible interventions being identified for pilot studies New paraquat formulation shown to be modestly safer following ingestion [38]. Animal studies suggest that solvents in agricultural OP insecticides may be important for toxicity [66]. Discussions with regulators and industry required to find pathway for implementing changes to formulation.
Personal – general	3.1 Improve resuscitation of patients 3.2 Improve use of gastric decontamination	Worked with colleagues to reduce the importance of gastric lavage and forced emesis in practice [33, 78]. RCT to show the effect of multiple dose activated charcoal [42, 45].
Personal – OP insecticides	4.1 Improve atropinization of patients 4.2 Improve use of oxime AChE reactivating drugs 4.3 Test whether a stoichiometric OP binder (e.g. BuChE) is beneficial 4.4 Test whether an OP hydrolase is beneficial 4.5 Prevent intermediate syndrome and long term ventilation	Reviewed international guidance [79] and proposed simplified system for patient resuscitation and stabilization by junior doctors [80]. Systematic reviews of oxime use for OP pesticide poisoning [53, 81] and clinical trial using multiple surrogate biomarkers to help inform interpretation of clinical outcomes [54]. Clinical trial planned for area where WHO Class I highly toxic OP insecticides are still in use. Animal study shows good pharmacodynamic effect of OpdA against several OP insecticides (in preparation). Clinical development planned. Clinical studies performed [82, 83]. Animal studies ongoing to identify mechanism and possible treatments.
Personal – oleander	5.1 Test efficacy of anti-digoxin Fab antidote 5.2 Improve availability of anti-digoxin Fab 5.3 Test effectiveness of flecainide treatment before pacing wire insertion to reduce risk of VT	RCT showed efficacy at reversing oleander-induced cardiotoxicity [30]; observational study suggested clinical benefit from its transient use [36]. Search for an affordable source of anti-digoxin Fab. Clinical study planned.

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