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The need for translational research on antidotes for pesticide poisoning

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Summary

1. Pesticide poisoning kills hundreds of thousands of people in the Asia Pacific region each year. The majority are from deliberate self-poisoning with organophosphorus pesticides (OP), aluminium phosphide and paraquat. The current response from a public health, medical and research perspective is inadequate.
2. There are few proven or effective treatments; in addition, very little clinical research has been done to transfer antidotes shown to work in animal studies into clinical practice.
3. The human toxicity of pesticides is poorly studied and better information might inform a more sustained and appropriate regulatory response. Further understanding may also lead to improvement in diagnosis and treatment.
4. The few effective treatments are not being recommended or delivered in an optimal and timely fashion to poisoned patients. A regional approach to facilitate appropriate pricing, packaging and delivery of antidotes is required.

Keywords

Keywords: Pesticide; poisoning; antidotes; paraquat; organophosphorus.

Introduction

Self-poisoning with pesticides is a major problem across the Asia Pacific region.1 It is estimated that hundreds of thousands of people die each year2, the majority from deliberate

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self-poisoning with organophosphorus pesticides (OP).3 Aluminium phosphide and paraquat are also responsible for many deaths in some areas.3 Although, the number of deaths indicates that this is a major public health problem, of the same order of magnitude as diabetes or HIV in many countries in the region, there is little coordinated effort being applied to improve the medical response to this problem. Only one antidote, atropine for OP poisoning, could be regarded as being of proven effectiveness.4 In this article we will describe further the requirements antidotes need to meet in order to be useful in practice and our experience with running clinical trials on pesticide antidotes in Sri Lanka. We will then argue the case for more translational research to progress antidotes that have been shown to be effective in animals into human trials and the need for research and planning for how best to provide and use these antidotes in the resource poor rural areas of Asia where pesticide poisoning is most important.

Antidotes - essential drugs or the quintessential distraction?

There are two areas where antidotes for pesticides are most relevant. The first is preparation for a response to the use of the closely-related chemical warfare agents or an acute chemical disaster.5 The second is the increasing recognition of the need for a coordinated response to the epidemic of deliberate self-poisoning in the Asia-Pacific region. To develop preparedness for chemical warfare agents, there are dedicated research facilities, large grant programs and extensive preparation within health services in the West. In particular there is substantial expenditure on antidotes, with around one billion dollars being spent in the US alone on preparation for terrorist use of chemical and biological weapons.6 This is in the setting of there having been less than 20 deaths from chemical terrorist events in the West in the last 25 years.7 It is also in stark contrast to the level of activity and support being given to find solutions to the problem of pesticide poisoning, where estimates suggest 20 people die in the world every 40 minutes.2 Furthermore, the stockpiling of antidotes for disasters has created new shortages and price rises causing further problems in providing access to antidotes for patients8,9 (which may lead to more rather than less deaths from poisoning).

The term ‘antidote’ implies almost magical properties in these drugs - a panacea for any chemical disaster. However, the previous occasions when chemical warfare agents have been used or there has been a major chemical disaster suggest the provision of more antidotes will make only a small difference to the outcome. In Bhopal, the Tokyo subway attack and the Iraqi use of multiple agents against Iran and their own Kurdish population, large numbers of casualties occurred from poisonings with recognised antidotes. However, the medical services were over-stretched with many people dying untreated at the scene and hundreds or thousands of patients presenting to hospitals within a few hours.10-12 It is debateable whether many more of our current antidotes could have been delivered even if they had been available in the nearest hospitals. If antidotes are to be useful in such a situation, they must:

1. be cheap enough to have large stocks available widely so that they could be used rapidly (as most deaths occur within a few hours).
2. have clear proof of their effectiveness and a known optimal dose
3. be able to be administered by relatively inexperienced medical, ambulance or nursing staff.
4. not require a high level of other medical infrastructure (as resources for intensive supportive care will be extremely stretched).
5. have available a simple diagnostic test or strategy to confirm the poisoning (many ‘symptomatic’ patients will not have been significantly poisoned).

6. have few adverse events when used under these conditions.

For example if we examine these modern experiences of chemical disasters and use of chemical weapons, we see that these criteria are not simple to meet. When terrorists released sarin in the Tokyo subway, there was widespread panic and confusion. Hospitals were flooded by many patients who subsequently were recognised not to have sarin toxicity but were probably suffering from anxiety. Despite initial stocks of antidotes being rapidly exhausted, only two patients died out of over 600 presenting to hospital.12 Moreover the initial report from the subway was that carbon monoxide or cyanide was involved. If large amounts of the cyanide antidote cobalt EDTA (Kelocyanor) had been used it is quite likely there would have been more rather than less casualties.

In contrast, in the examples from Iraq and Bhopal, there were massive numbers of deaths and seriously ill patients, and the most important limitation was providing any access to the most basic medical care. Multiple agents were involved on these occasions rendering even subsequent diagnosis of the causative agents difficult. 10,13,14

Such problems have parallels in pesticide poisoning in rural Asia and the Pacific. Access to medical care is often very limited and the requirements for a useful antidote (effective, safe, cheap, simple to use by those with limited training in a resource-poor situation aided by simple diagnostic tests) are almost identical to those required for a useful antidote in a response to a major chemical incident. However, the chances of people benefiting from such an antidote are far greater. Despite the millions of people affected each year, they usually present within a few hours to each hospital in potentially manageable numbers.3,15 Therefore a better antidote to use in the medical response could be both useful and deliverable. If we cannot demonstrate the effectiveness of antidotes in these settings, it is highly unlikely that they will be useful in the event of terrorist use of chemicals. The most likely agents to be used in a chemical weapon attack are anti-cholinesterase compounds like organophosphorus pesticides and ‘nerve agents’ such as sarin. There is an urgent need for better evidence on the effects of current treatments and also newer, more effective, antidotes.

The need for more translational research on pesticide antidotes.

Translational (“from bench to bedside”) research is the process of taking potentially useful drugs such as these through clinical development and then putting them into widespread use. 16-18 The current standard treatments for OP poisoning involve resuscitation, oxygen, atropine, oximes and diazepam. These are only partly effective, with a case fatality rate over 10% being common in most hospitals and some reporting much higher rates.3 The two other most commonly lethal pesticides, aluminium phosphide and paraquat, have case fatality rates over 50% and have no well established antidotes.19 Many antidotes for all three groups have been shown to work in ‘proof of concept’ animal research.20-26 However, those groups working on the animal research on these antidotes have generally not conducted any translational research.21

Translational research on antidotes for anticholinesterase poisoning.

The acute effects of OP pesticides are primarily due to the binding and subsequent inhibition of acetylcholinesterase (AChE) in synaptic clefts of the neuromuscular junction, autonomic nervous system, and CNS.27 The breakdown of acetylcholine is inhibited, resulting in sustained stimulation of post-synaptic receptors. The AChE may reactivate spontaneously or with the aid of oxime treatment. It may also become irreversibly bound (a phenomenon known as ‘ageing’).

Most widely used OP are ‘pro-poisons’ (usually thions) that require metabolism to much more toxic oxons. The parent compound, the metabolite and the OP-oxime complex are all broken down by ‘A-esterase’ enzymes such as OP hydrolase.

Deaths occur acutely due to respiratory failure or cardiovascular collapse, and later due to peripheral respiratory failure and complications of aspiration and long-term ventilation. These may be due to both peripheral and central actions of excessive acetylcholine, and may be partially mediated or modified by effects on glutamate and other non-cholinergic neurotransmitters.

The complexity of the toxicokinetic-dynamic pathophysiological process has implications for antidote development. First, to propose that efficacy and safety demonstrated in animal studies applies to humans makes many assumptions. This makes it critical to explore further the pathophysiology of OP poisoning in humans to see if extrapolation from animals is warranted and to test putative antidotes in human poisoning in clinical trials.

Second, this complex process provides many potential mechanisms for specific and non-specific antidotes. Animal studies have revealed many compounds offering clear benefits, yet no new treatment has been shown to work in clinical trials during the last thirty years. For example, in animal models, organophosphate (OP) hydrolases break down OPs and speed up reactivation of AChE. The use of such an enzyme to break down OPs in the blood might well make a fundamental difference in patient therapy. Such enzymes exist and have been shown to work in animal models for both prevention and treatment.22,23 There has been, however, little drive to start clinical studies.

Other potential OP antidotes include reversible anticholinesterases (eg. the carbamate pyridostigmine) which competitively bind to AChE and thereby prevent binding by OP28, and glutamate antagonists and agonists for adenosine and alpha-2 receptors which may limit damage to the central nervous system by non-specific mechanisms. 24-26 Diazepam is routinely used for the treatment of OP induced seizures, and can also be used to reduce agitation.4 However, in the absence of good information about the level of neuropathology in poisoned patients, it is not yet possible to determine the role of routine use of CNS sedatives such as diazepam, clonidine or NMDA blockers.4

A promising option may be sodium bicarbonate - a cheap widely used substance with supporting data from animal studies29-31 and a number of plausible mechanisms.32 Organophosphate hydrolase and acetylcholinesterase activity are pH dependent as is the activity of oximes and ageing of the OP-acetylcholinesterase complex. Bicarbonate is routinely used in Iran and Brasil for OP poisoning.32 However, the only randomized clinical trial to date had only 53 patients, and no trials have reported such striking results or been methodologically rigorous enough to justify adopting this treatment globally without further studies.32

Development of antidotes for pesticide poisoning in Asia - The South Asian Clinical Toxicology Research Collaboration (SACTRC)

SACTRC was set up in Sri Lanka in 2004 to address some of these deficiencies in the evidence and built on a previous collaboration between researchers from Oxford and Colombo Universities (Ox-Col). Our work has involved a range of studies, many of which are still underway. Although, there are several perspectives on priorities for drug development for OP poisoning, we have adopted an international health perspective by first testing whether currently used treatments are safe and effective and then moving on to trial broadly applicable interventions and new cheap antidotes. Our research includes systematic

reviews, pathophysiology studies, restrictions of pesticides, trials of new and established antidotes, and the pharmacoeconomics of antidotes.

Systematic reviews

We have conducted a number of evidence-based systematic reviews of treatments for pesticide poisoning.4,19,32,33 Each of these has revealed a lack of good evidence from clinical studies for effectiveness in pesticide-poisoned patients.

The life-saving effects of atropine are readily apparent within minutes in severely ill patients with OP poisoning and there is little doubt that this antidote has some efficacy. However, the improvement in survival with atropine in animal studies of OP poisoning is often less than that of oximes or diazepam (or indeed many experimental agents). Moreover, synergistic effects are usually noted with these and other antidotes.23,28

However, the clinical effectiveness of oximes such as pralidoxime is unknown.33 An RCT carried out at the Christian Medical College, Vellore, reported increased respiratory failure and death in patients who received 3-4g of pralidoxime/day as an infusion, but no loading dose.34 This result appears to contrast with mechanistic studies carried out in Germany that indicate that oximes readily reactivate AChE in humans.35,36 This discordance may be explained in part by the low dose of pralidoxime used and the long median delay of 12 hours between poisoning and hospital admission in Vellore.34 A twelve-hour delay to treatment allows the majority of AChE inhibited by dimethyl-OPs to become aged and unresponsive to oximes.

Recent studies (Eddleston & Eyer, unpublished) also suggest that AChE inhibited by S-alkyl OPs such as profenofos also ages very quickly and requires oxime therapy to be started within minutes, rather than hours. In the context of the rural developing world, this is not practical and such OPs may be best considered as not responding to pralidoxime. The long mean delay to hospital admission has the additional consequence of creating an opportunity for complications such as anoxia or aspiration to have occurred before hospital admission. Patients may then die of these complications which are not favourably influenced by oximes.

Randomised clinical trials of antidotes

In the context of a lack of evidence supporting current practice, our first priority has been to investigate the effectiveness of antidotes with a long history of use but no good data on effectiveness. This meant we could conduct definitive (Phase III) studies without exploratory work.

Although gastrointestinal decontamination is widely used, there are no data on effectiveness in pesticide poisoning and reviews of studies on other poisons have not revealed any evidence for clinical benefit.37 The most common pesticide group - OPs - is rapidly absorbed. Paraquat has very low bioavailability but peak concentrations still occur very early. Thus, gastric lavage and/or activated charcoal are only likely to work if given very soon after poisoning. In practice, however, they are used very frequently irrespective of the delay between poisoning and treatment.

There are many potential adverse events from lavage including inducing vagal responses, producing asystolic cardiac arrest and increased risk of pulmonary aspiration of the pesticide and it ’s solvent. To address the issue of the optimal method of gastrointestinal decontamination, we have conducted observational studies showing a favourable effect on outcome while we actively discouraged gastric emptying procedures - the case fatality rate dropping from 23% to 13% over two years. This was done in the context of conducting an

RCT in over 4000 patients comparing no gastrointestinal decontamination with single and multiple dose regimens of superactivated charcoal (ISRCTN02920054). Approximately half the patients enrolled had ingested pesticides and no net benefit from activated charcoal was seen.38 The full report of this trial should be published within a year.

We have also designed trials to address the uncertainty surrounding two promising treatments: oxime treatment for OP poisoning33 and high-dose immunosuppressant treatment for paraquat poisoning.19 Both of these treatments frequently cause adverse effects and trials are urgently needed to indicate whether the benefits outweigh the risks.

The WHO currently recommends a much higher loading dose of pralidoxime chloride (at least 30mg/kg given over 20-30 minutes followed by an infusion of at least 8mg/kg/hr) than was studied in the previous RCTs.39 A randomised controlled trial (RCT) in 1500 patients is now underway in Sri Lanka to test the effectiveness of this regimen against placebo in preventing death (ISRCTN55264358). We expect to commence a trial in 400 patients of immunosuppressant treatment for paraquat poisoning in late 2005. Both trials are anticipated to finish in 2008/9.

Phase II trials are small trials designed to provide preliminary evidence for efficacy and indicate the optimum dose. As most poisoning occurs in rural settings in the developing world, the ideal antidotes need to be as cheap, simple and stable as possible. Also, it is extremely useful if they are not patent protected, and have known safety in animals and humans, pharmacokinetic parameters and likely optimal dosing range. On this basis we have chosen sodium bicarbonate, clonidine, magnesium and diazepam as the first priority for further evaluation. All of these have a good biological rationale, positive evidence from animal studies26,29,39-42 and have been used in humans for many years.34-36,43-45

Observational Research.

A clinical database has been developed for all patients presenting to these centres. It is already apparent that studies based on this simple data may provide the best (non-RCT) evidence to many other questions - in particular those that might inform a more relevant approach to pesticide regulation.46 For example, within a short time new information has come to light on the clinical effects in overdose of new pesticides and the relative toxicity of different pesticides in human overdose.47-51 In many cases it is apparent that the animal LD50 is a very poor guide to the relative toxicity in hospitals for humans.50,52 This may be due to species differences or modifying effects of the availability and effectiveness of treatment.

There are also many areas where better understanding of the mechanisms and natural history of the poisoning might aid management. We will give examples of just two areas of major importance and immediate clinical relevance for further investigation.

Pathophysiology of OP poisoning

In addition to the well understood acute cholinergic effects of OP there are two well described syndromes of less certain pathophysiology that follow days to weeks after poisoning. The Intermediate Syndrome is a self-limited syndrome that comes on 1-4 days after ingestion and lasts 1-3 weeks.53 It is a disorder of the neuromuscular junction that occurs in the setting of prolonged acetylcholinesterase inhibition. It leads to paralysis and is a common cause of death in the developing world where access to long-term ventilation is rationed. Moreover, even when available, there is considerable morbidity and mortality from long-term ventilation. Despite its obvious clinical importance, no treatment has been shown to prevent or improve this poorly understood syndrome.

OP induced delayed neuropathy (OPIDN) is a large fibre predominantly motor peripheral neuropathy that comes on after some weeks and may last for years or never recover.54 It is often accompanied by long-term neurological damage elsewhere - upper motor neurone, neuropsychiatric, extrapyramidal and autonomic nervous system damage have all been documented.55

For both of these conditions there are many unanswered questions that might be answered with careful prospective data collection in a large cohort of patients (nearly all studies to date have had less than thirty patients and used only one investigation). For example, although it is believed that both these conditions occur more commonly with particular OPs, exactly which OPs cause the syndromes and the comparative incidence and severity has never been clarified. Other potential risk factors (e.g. age, gender, comorbidity, and initial severity of poisoning) have not been identified. The natural history of the pre-symptomatic stages has not been characterized (i.e. detectable abnormalities occurring before the development of the clinical syndromes). Consequently, there is no means of predicting which patients will develop them (which is necessary to efficiently test potential antidotes for preventing or ameliorating neurotoxicity).

Even less is known about the cardiotoxicity of OP pesticides and yet it is the leading cause of death in intensive care facilities.56 Between them the cardiotoxicity & neurotoxicity (Intermediate Syndrome & OPIDN) cause the majority of deaths and morbidity from OP pesticides.57

Predicting outcome in paraquat poisoning

Simple observational research will also be critical to advance our treatment of paraquat poisoning, a pesticide with a very high case fatality ratio and no proven treatment. Self-poisoning with paraquat is particularly common in parts of Asia, Pacific islands, and Caribbean.3 While many patients die rapidly, a proportion make an initial recovery only to succumb to fatal pulmonary fibrosis between 1 and 6 weeks later.

Most prediction of prognosis in paraquat poisoning has focused on paraquat concentrations. 19 While this is logical, the assay is not available in the rural centres where paraquat poisoning predominantly occurs. There are two main reasons for wanting a simple test that predicts a likely fatal outcome, especially for those who do not have a rapidly fatal outcome. First, it is clinically useful to be able to advise patients and institute appropriate palliative care. Second, it is this group that is most likely to respond to any antidotes. Evaluation of the effectiveness of treatment in non-randomised studies may be possible if a group with a nearly universally fatal outcome without treatment can be identified. These are also the group most appropriate to enrol in randomised clinical trials.

Practical issues in better provision of antidotes to the region

The use of antidotes in the region is beset by many problems. The first relates to the lack of applied research. Thus we believe there is a need for a number of specific clinical research programs based in a few countries in the region:

- to support and provide training in clinical management and research in pesticide poisoning
- to expand the evidence base in clinical toxicology of pesticides and management of deliberate self harm
- to examine the best methods to ensure that available evidence is adopted by clinicians.

The second problem of antidotes relates to the practical matters that do not seem specific to antidotes - The need to provide an adequate dose delivered in a timely manner to all patients based on need. There are many practical factors involved in this problem that covers the logistical issues of manufacture, delivery, storage, cost, cost-effectiveness, regulation, and product information and guidelines appropriate to the condition. However, while the problems are not confined to antidotes, there are some problems peculiar to antidotes. This was seen dramatically in the hording of oximes and subsequent price rises post September 11th.8,9 These antidotes have not been used and are now approaching their expiry dates throughout the West, but this hoarding resulted in shortages in the areas that actually had a real ongoing clinical use for them.

Many more problems with formulation, guidelines and supply are illustrated by atropine. Administration of the muscarinic antagonist atropine is fundamental to the management of OP poisoning.39 Its action at the synaptic cleft counters the effect of the increased level of acetylcholine in the parasympathetic nervous system, increasing the heart rate and blood pressure and reducing excess fluid and bronchospasm in the lungs.

The problem of providing adequate atropine in a timely fashion starts with failures in manufacturing and supply. Despite the need for an average loading dose of 25 mg (and often much more) in an unwell patient with OP poisoning, the standard commercial vial sizes range between 0.3 and 1.2 mgs: doses suitable for other indications but not designed for OP management. Yet in many parts of the developing world the most common indication for atropine would be OP poisoning.

Many guidelines on use are also manifestly deficient. Stabilisation of the patient requires rapid administration of intravenous atropine to improve cardiac and respiratory function - to ‘atropinise’ the patient.43 Although this has been standard practice for many years, the ideal regimen is still not known and there has been only one published controlled trial of atropine regimens.58. Ventilated OP patients who survive require substantial amounts of atropine.59 A recent review of textbook recommendations on patient atropinisation found 35 different recommendations.59

Most were not specific, suggesting doses of between 1 and 5mg, every 5-20 minutes; some would have required several hours to give a patient 25mg.

Insufficient stocking of available antidotes is also a widespread problem. The problem varies by country but is worst in the poorest and least developed countries, arguably those with the worst and most diverse toxicological problems. Some of these antidotes are extremely expensive, and unlikely to be affordable in many countries in the region with competing health priorities. The costs of one course of various antidotes is often greatly in excess of the annual per capita health expenditure for various countries in the region.60 (Table 1)

A further problem is the lack of information on what poisonings are occurring and therefore what antidotes are required. To address such problems requires a national approach to identify the types and amounts of antidotes required, the preferred manufacturers based on their price and quality of their product, the appropriate sites to hold less commonly used antidotes for distribution based on local infrastructure and transportation, and to develop from available antidotes appropriately modified guidelines for diagnosis and treatment. A regional collaboration using collective purchase arrangements could contribute to having an economic and effective means of ensuring a constant supply of antidotes in each country.

All these problems argue for a need to build more leadership and infrastructure in the region to conduct the necessary research and address the practical issues of affordability and delivery of antidotes & training. The appropriate international bodies to coordinate many

such developments are the International Program on Chemical Safety and The Asia Pacific Association of Medical Toxicology. These will need to be augmented by national coordination, most likely through regional poisons centres. And finally we believe there is a need for a number of clinical research and training centres of excellence within the region to increase the clinical evidence and skills.

Conclusions

The problem of pesticide poisoning in the region has clearly been shown to be an immense public health problem. However, in general the response has not been coordinated and has not dealt with systemic problems that prevent optimal care. In common with many other areas of medicine, some of the major barriers to better medical treatment with antidotes are the lack of 'translational research'.16-18 There is a complete lack of clinical research that establishes the role of treatments shown to be effective in animals. For a variety of complex reasons, there is also a widespread failure to implement the results of clinical research into routine practice. Focusing more research effort on these two rate-limiting steps is likely to be an efficient strategy for decreasing the burden of disease associated with pesticide poisoning in the Asia-Pacific region.

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Table 1

Costs (US$) of one course of selected antidotes and annual Health expenditure per capita in selected Asia-Pacific countries.60

Cost/treatment (US$)	Antidote *	Asia-Pacific Countries with annual per capita health expenditure in this range.
>$10	Sodium Bicarbonate	Afghanistan, Laos
$10-20	Activated charcoal in suspension.	Bangladesh, Indonesia,
	Naloxone	Nepal, Pakistan
$20-50	Atropine (low dose)	Cambodia, China, India,Papua New Guinea,Mongolia, Philippines, SriLanka, Vietnam
$50-200	Atropine (high dose)	Fiji, Malaysia, Maldives,
	Pyridoxine	Myanmar, Samoa, Thailand,
	Succimer	Tonga
	Cyclophosphamide/Methyprednisolone	
	Flumazenil	
	Acetylcysteine	
$200-1000	Pralidoxime (low dose)	Singapore, South Korea
	Desferroxamine	
	Hydroxocobalamin	
>$1000	Digoxin binding Fab antibodies,	Australia, New Zealand,
	Pralidoxime (high dose)	Japan

* based on dose required in one severe adult poisoning - Australian Wholesale prices-December 2004