Integrating approaches to paraquat poisoning

Late last year in a hospital in the North Central Province, there was a 16-year old girl who had swallowed a mouthful of paraquat immediately following an argument with her parents. The paraquat had been stored inside her house. She was cyanosed and apparently within hours or days of death, having suffered a fortnight of steadily increasing breathlessness. She could not eat or sleep because of dyspnoea, and even had difficulty drinking. She was frightened and no longer wished to die, if indeed she had ever wanted to. This tragic scenario is not uncommon, there are about 400-500 deaths each year in Sri Lanka from paraquat poisoning and tens of thousands worldwide. The majority of agrochemical poisonings are impulsive ingestions of chemicals stored in or near the home. In Sri Lanka the ingestion of paraquat has about 65% mortality [1], much higher than any other agrochemical. Unlike other agrochemicals, paraquat has no proven antidote, and supportive care is relatively ineffective at preventing death. The amount of paraquat absorbed is a key factor in determining outcome, hence the prognostic importance of blood concentration.

A substantial reduction of poisoning deaths is unlikely to be achieved by focusing solely on in-hospital care. The integration of evidence-based interventions at multiple points in the chain of events leading up to and following the poisoning is more likely to produce sustained improvement [2]. Where does paraquat fit within such a scheme in Sri Lanka?

Paraquat deaths would cease if it was banned. However, few countries have banned it completely. Paraquat is cheap and may have other advantages from an agricultural perspective over other herbicides. There are some primary prevention strategies that are currently being considered. Removal of pesticides from the home and/or storage in lockable containers underpins the safe storage strategies promoted by FAO, WHO and the agrochemical industry. These require further evaluation, as they are not supported by any evidence of long term effectiveness in reducing poisoning and have many potential pitfalls [3]. Safe storage requires continuing active participation from the users. Pilot projects in Sri Lanka suggest that the provision of safe storage devices changes the way pesticides are stored. Six months after lockable boxes were provided most pesticides were being stored in the locked box. However, this was associated with a huge reduction in the storage of pesticides in the fields (42% to 2 %) and a corresponding increase in pesticide storage in homes. Therefore this change in storage patterns could potentially (paradoxically) increase the risk of pesticide poisoning, especially if the safe storage boxes are damaged or not kept secure [4]. Further research is required to develop the best method of safe storage, ideally one that can be used to store pesticides in the field.

Development of formulations that reduce the likelihood of ingestion or toxicity has a long history. For many years most formulations have added stenching agents, emetics and purgatives, without much obvious benefit. There are two new developments in this area in Sri Lanka. A new formulation of paraquat (Inteon™) was developed with more emetics and an alginate (an agent designed to form a gel which traps the paraquat in the stomach). This led to a modest reduction in mortality (from 75% to 65%) [1]. Another change in the Inteon™ formulation, shown to reduce toxicity further in animal studies, is currently marketed and being evaluated in Sri Lanka and Korea. Even the most optimistic projections for this formulation suggest that mortality will remain well over 50% so further regulatory approaches need to be considered. Any regulatory approach needs to be evaluated by ongoing assessment of human toxicity of both the compound and any substitutes used in the field.

The big question is: What is an 'acceptable level' of human toxicity? Zero mortality is probably an unachievable goal since all pesticides have some mortality even if it is only due to the surfactants and solvents or medical complications such as aspiration pneumonia. A pragmatic approach may be to examine the mortality rates of other products used for similar indications in agriculture and use the lowest mortality as the benchmark for product registration. For example, the other commonly used herbicides (propanil, glyphosate and MCPA) have a mortality of between 4% and 8%. To reduce paraquat mortality to a similar rate would require both reductions in product concentration and reformulation. In October 2006 the Pesticide Registrar mandated a reduction in paraquat concentration for some brands, from 20% to 6.5%, and also restricted the bottle size. These restrictions have not yet been placed on Inteon™ products, but are expected to further reduce mortality. Both these interventions are likely to increase to some extent the cost of paraquat.

Using mortality as the sole benchmark has its limitations. Any comparison between two agents needs to consider the costs of treatment and the costs of long term morbidity such as pulmonary fibrosis.

At present the only accepted treatment for paraquat poisoning is gastrointestinal decontamination with either Fuller's earth or activated charcoal. Over half the patients vomit within 15 minutes of ingestion [1]. Gastric lavage is unlikely to be effective and is relatively contraindicated following ingestion of corrosive substances like paraquat. Further, induction of emesis is also unlikely to have much benefit and may delay treatment with adsorbents (charcoal or Fuller's earth). The benefit of adsorbent agents is greatest if they are given within an hour of ingestion, at a time when some of the poison is still in the stomach. A recent study has shown that adsorbents are given infrequently in the peripheral hospitals where patients most

commonly present. In fact 30% of these hospitals in the North Central Province did not have stocks of either Fuller's Earth or charcoal [5]. These agents are usually given some hours later in secondary referral hospitals. It follows that a transfer of adsorptive agents from secondary to peripheral hospitals would not generate additional costs but might substantially improve efficacy.

There are potential antidotes that need evaluation. Perhaps the two most promising are immunosuppression and anti-oxidants. Immunosuppression with high-dose cyclophosphamide and methylprednisolone followed by dexamethasone has been suggested as moderately effective treatment in a number of small studies [6-9]. However, there are a number of methodological flaws in these studies, which both increases the risk that bias explains the results and makes it difficult to determine which patients might benefit. Some clinicians are using a variety of immunosuppression protocols within Sri Lanka. Immunosuppressants are expensive and their intrinsic toxicity has potential for further increasing mortality. We believe the widespread use of this treatment is premature. A multi-centre randomised clinical trial is now underway in Sri Lanka to see if immunosuppressant is effective, safe and which patients will benefit.

The primary mechanism of paraquat toxicity is uncontrolled production of free radicals. Neutrophils contribute to this production and it occurs particularly in the lungs where certain cells actively take up paraquat. Clinicians have tried a number of anti-oxidant and anti-neutrophil treatments in the hope that they might interfere with the process [10, 11]. These treatments have minimal toxicity and a lower cost when compared with immunosuppressants. Anti-oxidants have shown some beneficial effects in animal studies of paraquat poisoning. However, the benefits in animal studies for each agent have been only modest. These treatments include allopurinol, vitamins C and E, N-acetylcysteine, low-dose corticosteroids and nitrous oxide. None have been rigorously examined in clinical trials [11], but human data on anti-oxidants does support doing further studies. Vitamin C (2000 mg loading dose followed by an infusion of 4000 mg/day) was given to five patients all of whom survived despite moderately severe poisoning [12]. S-carboxymethylcysteine (1500 mg/day for 3 weeks), a glutathione precursor, was given to 35 patients and 77% of patients survived [13]. Dexamethasone has been used along with more toxic immunosupresssant treatments by a number of groups [10]. It may also induce p-glycoprotein, which actively transports paraquat out of alveolar cells [14].

Much more work is required to see if these agents combined can significantly reduce markers of oxidative stress or clinical features in acute paraquat poisoning. Potentially they may be synergistic, as there are several sources for oxygen free radical production. Then the combination of agents that appears most effective will also need to be evaluated in a large clinical trial to see if this translates into a significant reduction in mortality. Any treatment developed must also be evaluated for accessibility and affordability for patients.

There are a number of other interventions worth pursuing, in particular some focused on reducing all self-poisonings, such as improving coping skills, or addressing the role of alcohol in many self-poisonings. We strongly believe that a combination of strategies to reduce self-poisonings, reduced access to the most toxic products, reduced toxicity of formulations and improved treatment will have additive effects in reducing harm from paraquat (and other pesticides) [2]. We have outlined how SACTRC is examining some of these in the context of paraquat poisoning. There are a number of other research groups in Sri Lanka evaluating other approaches and other pesticides. All of us will rely on the active participation of clinicians in Sri Lanka to eventually reduce the number of people dying from the slow torture that is paraquat poisoning.

Acknowledgements

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