



IASP Special Interest Group (SIG) on the Prevention of Intentional Pesticide Poisoning

Bibliography: Study Design - Experimental

Afshari, R., M. Mohammadi, et al. (2010). "Therapeutic effects of sodium bicarbonate in organophosphate poisoning in man is pH dependent: A randomized clinical trial." Toxicology Letters **Conference: 12th International Congress of Toxicology Barcelona Spain. Conference Start: 20100719 Conference End: 20100723. Conference Publication: (var.pagings). 196: S84-S85.**

Introduction: Organophosphate (OP) pesticides are widely used across the globe. Intentional and accidental overdoses with OPs are common in this country [1]. High doses of sodium bicarbonate have shown to be effective in OP poisoning in man [2,3]. This study aimed at comparing the therapeutic effects of sodium bicarbonate with lower doses with or without adding magnesium sulphate on organophosphate poisoning. Methods: All subjects with alleged OP poisoning (excluding mild cases) were studied prospectively from May 2008 to September 2009. Ethics approval was obtained (MUMS-84386). These subjects were randomly allocated into 4 groups: 1. Low dose sodium bicarbonate (S). 2. Low dose magnesium sulphate (M). 3. Both (B) and 4. none (N). All cases received fluids and atropine as well as diazepam if needed. Results: 27 S, 25 M, 27 B and 26 N subjects were studied. Age, gender and severity of poisoning were not significantly different in these four groups. Mean (SD) pH level was on average 7.33 (0.08). There were no significant differences between S or S and B in comparison to others in regard to mean duration of admission, diazepam administration, seizure, atropine administration, mechanical ventilation, ICU admission and deaths. Conclusion: Despite previous positive reports with high doses of SB, lower doses is not capable of improving outcomes of OP poisoning especially if pH is not higher than a 7.33. Still high doses are recommended.

Buckley, N. A., M. Eddleston, et al. (2005). "Oximes for acute organophosphate pesticide poisoning." Cochrane Database Syst Rev(1): CD005085.

BACKGROUND: Acute organophosphorus pesticide poisoning causes tens of thousands of deaths each year across the developing world. Standard treatment involves administration of intravenous atropine and oxime to counter acetylcholinesterase inhibition at the synapse. The usefulness of oximes, such as pralidoxime and obidoxime, has been challenged over the past 20 years by physicians in many parts of the world, who have failed to see benefit in their clinical practice. OBJECTIVES: To find the clinical trial evidence for oximes producing clinical benefit in acute organophosphorus pesticide-poisoned patients. SEARCH STRATEGY: We carried out a systematic search to find randomised clinical trials (RCTs) of oximes in acute organophosphorus pesticide poisoning, using MEDLINE, EMBASE and Cochrane databases. All articles with the text words 'organophosphate' or 'oxime' together with 'poisoning' or 'overdose' were examined. (Search last updated November 2003.) SELECTION CRITERIA: Articles that could possibly be randomised clinical trials were retrieved to determine if this was the case. DATA COLLECTION AND ANALYSIS: The published methodology of the possible RCTs located is not clear. One was found in abstract form only and two other published trials also had many gaps in the published methodology. We have attempted to contact the principal authors of all three trials but have been unable to obtain further information. MAIN RESULTS: Two RCTs have been published, involving 182 patients treated with pralidoxime. These trials did not find benefit. However, the studies did not

take into account a number of issues important for outcome and the methodology is unclear. Therefore, a generalised statement on effectiveness cannot be supported by the published results. In particular, characteristics at baseline were not evenly balanced, the dose of oxime was much lower than recommended in guidelines, there were substantial delays to treatment, and the type of organophosphate was not taken into account. The abstract of the third trial, a small possible RCT, is uninterpretable without further data. **AUTHORS' CONCLUSIONS:** Current evidence is insufficient to indicate whether oximes are harmful or beneficial in the management of acute organophosphorus pesticide poisoning. A much larger RCT is required to compare the World Health Organization recommended pralidoxime regimen (>30 mg/kg bolus followed by >8 mg/kg/hr infusion) with placebo. There are many theoretical and practical reasons why oximes may not be useful to patients with overwhelming self-poisoning. Such a study will need to be designed with pre-defined sub-group analysis to allow identification of patient sub-groups that may benefit from oximes.

Eddleston, M., P. Eyer, et al. (2009). "Pralidoxime in acute organophosphorus insecticide poisoning--a randomised controlled trial." *PLoS Med* **6**(6): e1000104. **BACKGROUND:** Poisoning with organophosphorus (OP) insecticides is a major global public health problem, causing an estimated 200,000 deaths each year. Although the World Health Organization recommends use of pralidoxime, this antidote's effectiveness remains unclear. We aimed to determine whether the addition of pralidoxime chloride to atropine and supportive care offers benefit. **METHODS AND FINDINGS:** We performed a double-blind randomised placebo-controlled trial of pralidoxime chloride (2 g loading dose over 20 min, followed by a constant infusion of 0.5 g/h for up to 7 d) versus saline in patients with organophosphorus insecticide self-poisoning. Mortality was the primary outcome; secondary outcomes included intubation, duration of intubation, and time to death. We measured baseline markers of exposure and pharmacodynamic markers of response to aid interpretation of clinical outcomes. Two hundred thirty-five patients were randomised to receive pralidoxime (121) or saline placebo (114). Pralidoxime produced substantial and moderate red cell acetylcholinesterase reactivation in patients poisoned by diethyl and dimethyl compounds, respectively. Mortality was nonsignificantly higher in patients receiving pralidoxime: 30/121 (24.8%) receiving pralidoxime died, compared with 18/114 (15.8%) receiving placebo (adjusted hazard ratio [HR] 1.69, 95% confidence interval [CI] 0.88-3.26, $p = 0.12$). Incorporating the baseline amount of acetylcholinesterase already aged and plasma OP concentration into the analysis increased the HR for patients receiving pralidoxime compared to placebo, further decreasing the likelihood that pralidoxime 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]). To reduce confounding due to ingestion of different insecticides, we further analysed patients with confirmed chlorpyrifos or dimethoate poisoning alone, finding no evidence of benefit. **CONCLUSIONS:** Despite clear reactivation of red cell acetylcholinesterase in diethyl organophosphorus pesticide poisoned patients, we found no evidence that this regimen improves survival or reduces need for intubation in patients with organophosphorus insecticide

poisoning. The reason for this failure to benefit patients was not apparent. Further studies of different dose regimens or different oximes are required.

Eddleston, M., E. Juszczak, et al. (2008). "Multiple-dose activated charcoal in acute self-poisoning: a randomised controlled trial." *Lancet* **371**(9612): 579-587.

BACKGROUND: The case-fatality for intentional self-poisoning in the rural developing world is 10-50-fold higher than that in industrialised countries, mostly because of the use of highly toxic pesticides and plants. We therefore aimed to assess whether routine treatment with multiple-dose activated charcoal, to interrupt enterovascular or enterohepatic circulations, offers benefit compared with no charcoal in such an environment. **METHODS:** We did an open-label, parallel group, randomised, controlled trial of six 50 g doses of activated charcoal at 4-h intervals versus no charcoal versus one 50 g dose of activated charcoal in three Sri Lankan hospitals. 4632 patients were randomised to receive no charcoal (n=1554), one dose of charcoal (n=1545), or six doses of charcoal (n=1533); outcomes were available for 4629 patients. 2338 (51%) individuals had ingested pesticides, whereas 1647 (36%) had ingested yellow oleander (*Thevetia peruviana*) seeds. Mortality was the primary outcome measure. Analysis was by intention to treat. The trial is registered with controlled-trials.com as ISRCTN02920054. **FINDINGS:** Mortality did not differ between the groups. 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). No differences were noted for patients who took particular poisons, were severely ill on admission, or who presented early. **INTERPRETATION:** We cannot recommend the routine use of multiple-dose activated charcoal in rural Asia Pacific; although further studies of early charcoal administration might be useful, effective affordable treatments are urgently needed.

Eddleston, M., L. Szinicz, et al. (2002). "Oximes in acute organophosphorus pesticide poisoning: a systematic review of clinical trials." *QJM* **95**(5): 275-283.

BACKGROUND: Acute organophosphorus (OP) pesticide poisoning is widespread in the developing world. Standard treatment involves the administration of intravenous atropine and an oxime to counter acetylcholinesterase inhibition at the synapse, but the usefulness of oximes is uncertain. **AIM:** To assess the evidence on the use of oximes in OP poisoning. **DESIGN:** Systematic review. **METHODS:** We searched Medline, Embase, and Cochrane databases (last check 01/02/02) for 'organophosphate' or 'oxime' together with 'poisoning' or 'overdose'. We cross-referenced from other articles, and contacted experts to identify unpublished studies. A Web search engine [www.google.com] was also used, with the keywords 'organophosphate', 'oxime', and 'trial' (last check 01 02/02). **RESULTS:** We found two randomized controlled trials (RCTs) involving 182 patients treated with pralidoxime. The RCTs found no benefit with pralidoxime, and have been used to argue that pralidoxime should not be used in OP poisoning. **DISCUSSION:** The RCT authors must be congratulated for attempting important studies in a difficult environment. However, their studies did not take into account recently clarified issues regarding outcome, and their methodology is unclear. A generalized statement that pralidoxime should not be used in OP poisoning is not

supported by the published results. Oximes may well be irrelevant in the overwhelming self-poisoning typical of the tropics, but a large RCT comparing the current WHO-recommended pralidoxime regimen (>30 mg/kg bolus followed by >8 mg/kg/h infusion) with placebo is needed for a definitive answer. Such a study should be designed to identify any patient subgroups that might benefit from oximes.

Eddleston, M., M. F. Wilks, et al. (2003). "Prospects for treatment of paraquat-induced lung fibrosis with immunosuppressive drugs and the need for better prediction of outcome: a systematic review." *QJM* **96**(11): 809-824.

BACKGROUND: Acute paraquat self-poisoning is a significant problem in parts of Asia, the Pacific and the Caribbean. Ingestion of large amounts of paraquat results in rapid death, but smaller doses often cause a delayed lung fibrosis that is usually fatal. Anti-neutrophil ('immunosuppressive') treatment has been recommended to prevent lung fibrosis, but there is no consensus on efficacy. **Aim:** To review the evidence for the use of immunosuppression in paraquat poisoning, and to identify validated prognostic systems that would allow the use of data from historical control studies and the future identification of patients who might benefit from immunosuppression. **DESIGN:** Systematic review. **METHODS:** We searched PubMed, Embase and Cochrane databases for 'paraquat' together with 'poisoning' or 'overdose'. We cross-checked references and contacted experts, and searched on [www.google.com] and [www.yahoo.com] using 'paraquat', 'cyclophosphamide', 'methylprednisolone' and 'prognosis'. **RESULTS:** We found ten clinical studies of immunosuppression in paraquat poisoning. One was a randomized controlled trial (RCT). Seven used historical controls only; the other two were small (n = 1 and n = 4). Mortality in controls and patients varied markedly between studies. Three of the seven non-RCT controlled studies measured plasma paraquat; analysis using Proudfoot's or Hart's nomograms did not suggest that immunosuppression increased survival in these studies. Of 16 prognostic systems for paraquat poisoning, none has been independently validated in a large cohort. **DISCUSSION:** The authors of the RCT have performed valuable and difficult research, but their results are hypothesis-forming rather than conclusive; elsewhere, the use of historical controls is problematic. In the absence of a validated prognostic marker, a large RCT of immunosuppression using death as the primary outcome is required. This RCT should also prospectively test and validate the available prognostic methods, so that future patients can be selected for this and other therapies on admission.

Gawarammana, I., N. A. Buckley, et al. (2012). "A randomised controlled trial of high-dose immunosuppression in paraquat poisoning." *Clinical Toxicology*
Conference: 2012 International Congress of the European Association of Poisons Centres and Clinical Toxicologists, EAPCCT 2012 London United Kingdom. Conference Start: 20120525 Conference End: 20120601. Conference Publication: (var.pagings). 50 (4): 278.

Objective: Intentional self-poisoning with paraquat herbicides is a major problem in rural Asia, and the Pacific. Paraquat self poisoning has the highest recorded case fatality (~70%) for a pesticide. There is no proven antidote, however, immunosuppression with cyclophosphamide,

methylprednisolone and dexamethasone has widely become the treatment of choice in many parts of the world. However, evidence of clinical benefit is weak. We aimed to determine whether the addition of immunosuppression to supportive care offers benefit in resource poor Asian district hospitals. **Methods:** We compared immunosuppression (cyclophosphamide up to 1 g day for two days, methylprednisolone 1 g/day for 3 days and dexamethasone 8 mg three times a day for 14 days) with saline and placebo tablets in a double-blind randomised placebocontrolled trial. Mortality at 3 months was the primary outcome. **Results:** The trial was stopped early as paraquat was banned in Sri Lanka. At this time, there were 605 patients with a history of paraquat ingestion. There were 407 who met inclusion criteria. Two hundred and ninety-eight patients consented and were randomised to receive immunosuppression or saline and placebo. Overall mortality in the trial was 208/298 (69.8%). There was no difference in case fatality between patients in placebo group (108/152 [71.05%]) and immunosuppression group (100/146 [68.4%]). (Difference between fractions 2.5%, 95% CI: -7 - 12). There was also no difference in median time to death between the placebo group and the immunosuppression group (2 days vs 1.92 days respectively). **Conclusion:** We found no evidence that this immunosuppression regimen improves survival in paraquat poisoned patients and thus this popular treatment should no longer be recommended.

Gunnell, D., M. Eddleston, et al. (2007). "The global distribution of fatal pesticide self-poisoning: systematic review." *BMC Public Health* 7: 357.

BACKGROUND: Evidence is accumulating that pesticide self-poisoning is one of the most commonly used methods of suicide worldwide, but the magnitude of the problem and the global distribution of these deaths is unknown. **METHODS:** We have systematically reviewed the worldwide literature to estimate the number of pesticide suicides in each of the World Health Organisation's six regions and the global burden of fatal self-poisoning with pesticides. We used the following data sources: Medline, EMBASE and psycINFO (1990-2007), papers cited in publications retrieved, the worldwide web (using Google) and our personal collections of papers and books. Our aim was to identify papers enabling us to estimate the proportion of a country's suicides due to pesticide self-poisoning. **RESULTS:** We conservatively estimate that there are 258,234 (plausible range 233,997 to 325,907) deaths from pesticide self-poisoning worldwide each year, accounting for 30% (range 27% to 37%) of suicides globally. Official data from India probably underestimate the incidence of suicides; applying evidence-based corrections to India's official data, our estimate for world suicides using pesticides increases to 371,594 (range 347,357 to 439,267). The proportion of all suicides using pesticides varies from 4% in the European Region to over 50% in the Western Pacific Region but this proportion is not concordant with the volume of pesticides sold in each region; it is the pattern of pesticide use and the toxicity of the products, not the quantity used, that influences the likelihood they will be used in acts of fatal self-harm. **CONCLUSION:** Pesticide self-poisoning accounts for about one-third of the world's suicides. Epidemiological and toxicological data suggest that many of these deaths might be prevented if (a) the use of pesticides most toxic to humans was restricted, (b) pesticides could be safely

stored in rural communities, and (c) the accessibility and quality of care for poisoning could be improved.

Karalliedde, L. and N. Senanayake (1989). "Organophosphorus insecticide poisoning." British Journal of Anaesthesia **63 (6)**: 736-750.

Organophosphorus agents are used world wide in increasing quantities for the control of insects affecting agriculture. These agents are used also for disease vector control. OP agents became important during World War II for their potential use in chemical warfare. Disease in man caused by these agents is causing much concern, particularly in the developing agricultural countries. OP compounds produce toxicity following systemic absorption from the skin and mucous membranes. Ingestion with suicidal intent or accidentally following contamination of food by these agents is a common mode of intoxication. Intoxication associated with occupational exposure (formulating, mixing, handling, spraying) usually follows absorption either through the skin or by inhalation. The acute cholinergic crisis which immediately follows intoxication is caused by phosphorylation and inhibition of AChE. The muscarinic and nicotinic manifestations of ACh accumulation produce a clinical syndrome which frequently requires urgent resuscitation and therapy in intensive care units. The need for ventilatory care following recovery from the cholinergic phase was emphasized recently following recognition of the 'Intermediate Syndrome' (IMS). The IMS corresponds closely to the sequence of myopathic changes observed in animal experiments following OP intoxication. Delayed polyneuropathy caused possibly by ageing of the phosphorylated NTE occurs usually 2-4 weeks after intoxication. The distribution of muscle weakness of the delayed polyneuropathy is distinct from that seen in IMS. Cholinergic crisis and IMS present with life threatening complications. Ventilatory care is required in both situations; in view of the development of IMS it is necessary to observe all patients for at least 5 days after intoxication. There is growing concern regarding the effects of chronic exposure in man. The International Agency for Research in Cancer (IARC) concluded in 1983 that there was little evidence of strong mutagenic or carcinogenic effects in mammals from five widely used insecticides (malathion, methyl parathion, parathion, tetrachlorvinphos and trichlorfon). However, controversy exists in interpretation of the studies on which the IARC conclusions were based. With the widespread use of these agents, effects of prolonged exposure on teratogenicity, carcinogenicity and reproductive function will be important areas of study. In view of the effect of OP agents on enzymes, drug sensitivities such as those observed with suxamethonium will become evident. Another group of drugs that may be affected similarly are the local anaesthetics, as the amino esters are usually hydrolysed in plasma by pseudocholinesterase. There is great emphasis on preventive measures and on the use of alternatives to insecticides in agriculture. At present, the goal of safe and effective use of insecticides is achieved best by an agromedical approach to pesticide management - integrated, interdisciplinary application of the skills and knowledge of agriculture, applied chemistry and medicine.

Li, L. R., E. Sydenham, et al. (2010). "Glucocorticoid with cyclophosphamide for paraquat-induced lung fibrosis." Cochrane Database Syst Rev(6): CD008084.

BACKGROUND: Paraquat is an effective and widely used herbicide but is also a lethal poison. In many developing countries paraquat is widely available and inexpensive, making poisoning prevention difficult. However most of the people who become poisoned from paraquat have taken it as a means of suicide. Standard treatment for paraquat poisoning both prevents further absorption and reduces the load of paraquat in the blood through haemoperfusion or haemodialysis. The effectiveness of standard treatments is extremely limited. The immune system plays an important role in exacerbating paraquat-induced lung fibrosis. Immunosuppressive treatment using glucocorticoid and cyclophosphamide in combination is being developed and studied. **OBJECTIVES:** To assess the effects of glucocorticoid with cyclophosphamide on mortality in patients with paraquat-induced lung fibrosis. **SEARCH STRATEGY:** To identify randomised controlled trials on this topic, we searched the Cochrane Injuries Group's Specialised Register (searched 15 Sept 2009), CENTRAL (The Cochrane Library 2009, Issue 3), MEDLINE (Ovid SP) (1950 September Week 1 2009), EMBASE (Ovid SP) (1980 to 2009 Week 37), ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) (1970 to Sept 2009), ISI Web of Science: Conference Proceedings Citation Index - Science (CPCI-S) (1990 to Sept 2009), Chinese bio-medical literature & retrieval system (CBM) (1978 to Sept 2009), Chinese medical current contents (CMCC) (1995 to Sept 2009), and Chinese medical academic conference (CMAC) (1994-Sept 2009). The searches were completed in September 2009. **SELECTION CRITERIA:** Randomised controlled trials (RCTs) were included in this review. All patients were to receive standard care, plus the intervention or control. The intervention was glucocorticoid with cyclophosphamide in combination versus a control of a placebo, standard care alone, or any other therapy in addition to standard care. **DATA COLLECTION AND ANALYSIS:** The mortality risk ratio (RR) and 95% confidence interval (CI) was calculated for each study on an intention-to-treat basis. Data for all-cause mortality at final follow-up were summarised in a meta-analysis using a fixed-effects model. **MAIN RESULTS:** This systematic review includes three trials with a combined total of 164 participants who had moderate to severe paraquat poisoning. Patients who received glucocorticoid with cyclophosphamide in addition to standard care had a lower risk of death at final follow-up than those receiving standard care only (RR 0.72 (95% CI 0.59 to 0.89)). **AUTHORS' CONCLUSIONS:** Based on the findings of three small RCTs of moderate to severely poisoned patients, glucocorticoid with cyclophosphamide in addition to standard care may be a beneficial treatment for patients with paraquat-induced lung fibrosis. To enable further study of the effects of glucocorticoid with cyclophosphamide for patients with moderate to severe paraquat poisoning, hospitals may provide this treatment as part of an RCT with allocation concealment.

Li, Y., M. L. Tse, et al. (2009). "Systematic review of controlled clinical trials of gastric lavage in acute organophosphorus pesticide poisoning." *Clin Toxicol (Phila)* **47**(3): 179-192.

BACKGROUND: Organophosphorus pesticide (OP) self-poisoning is a major problem in the developing rural world. There is little clinical trial data to guide therapy, hindering the identification of best therapy. Despite the recognition

of adverse effects, gastric lavage is commonly done in Asia. We aimed to identify studies assessing its effectiveness. **METHOD:** We systematically searched the literature for controlled clinical studies that assessed the effect of gastric lavage in OP pesticide self-poisoning. **RESULTS:** All 56 studies identified were Chinese and reported benefit from the intervention studied, including multiple gastric lavages, use of norepinephrine or pralidoxime in the lavage fluid, concurrent treatment with naloxone or scopolamine, insertion of the gastric tube via a laparotomy incision, and lavage later than 12 h post-ingestion. However, only 23 were RCTs and none presented adequate methodology for their quality to be assessed. The patient population and study treatment protocol were not defined - large variation in case fatality in the control arm of the studies (from 4.5 to 93%) suggests marked variation between studies and likely between study arms. No study compared an intervention against a control group receiving no gastric lavage or provided any data to indicate whether a significant quantity of poison was removed. **CONCLUSION:** Despite widespread use of multiple gastric lavages for OP pesticide poisoning across Asia, there is currently no high-quality evidence to support its clinical effectiveness. There is a need for studies to identify in which patients and for what duration gastric lavage is able to remove significant quantities of poison. Following these studies, large clinical trials will be required to address the effectiveness and safety of gastric lavage (either single or multiple) in acute OP pesticide poisoning.

Li, Y., X. Yu, et al. (2006). "Gastric lavage in acute organophosphorus pesticide poisoning (GLAOP)--a randomised controlled trial of multiple vs. single gastric lavage in unselected acute organophosphorus pesticide poisoning." BMC Emerg Med **6**: 10.

BACKGROUND: Organophosphorus (OP) pesticide poisoning is the most common form of pesticide poisoning in many Asian countries. Guidelines in western countries for management of poisoning indicate that gastric lavage should be performed only if two criteria are met: within one hour of poison ingestion and substantial ingested amount. But the evidence on which these guidelines are based is from medicine overdoses in developed countries and may be irrelevant to OP poisoning in Asia. Chinese clinical experience suggests that OP remains in the stomach for several hours or even days after ingestion. Thus, there may be reasons for doing single or multiple gastric lavages for OP poisoning. There have been no randomised controlled trials (RCTs) to assess this practice of multiple lavages. Since it is currently standard therapy in China, we cannot perform a RCT of no lavage vs. a single lavage vs. multiple lavages. We will compare a single gastric lavage with three gastric lavages as the first stage to assess the role of gastric lavage in OP poisoning. **METHODS/DESIGN:** We have designed an RCT assessing the effectiveness of multiple gastric lavages in adult OP self-poisoning patients admitted to three Chinese hospitals within 12 hrs of ingestion. Patients will be randomised to standard treatment plus either a single gastric lavage on admission or three gastric lavages at four hour intervals. The primary outcome is in-hospital mortality. Analysis will be on an intention-to-treat basis. On the basis of the historical incidence of OP at the study sites, we expect to enroll 908 patients over three years. This projected sample size provides sufficient power to evaluate the death rate; and a

variety of other exposure and outcome variables, including particular OPs and ingestion time. Changes of OP level will be analyzed in order to provide some toxic kinetic data. DISCUSSION: the GLAOP study is a novel, prospective cohort study that will explore to the toxic kinetics of OP and effects of gastric lavage on it. Given the poor information about the impact of gastric lavage on clinical outcomes for OP patients, this study can provide important information to inform clinical practice.

Mohammadi, M., R. Afshari, et al. (2010). "Therapeutic effects of sodium bicarbonate and magnesium sulphate in organophosphate poisoning: A randomized clinical trial." *Clinical Toxicology Conference: 2010 International Congress of the European Association of Poisons Centres and Clinical Toxicologists Bordeaux France. Conference Start: 20100511 Conference End: 20100514. Conference Publication: (var.pagings). 48 (3): 297.*

Objective: Organophosphate (OP) pesticides are widely used in agricultural settings. Intentional and accidental overdoses with these agents are common in this country. This study was aimed at comparing the therapeutic effects of sodium bicarbonate and magnesium sulphate on organophosphate poisoning. Methods: All consenting subjects with alleged moderate to severe acute organophosphate poisoning from May 2008 to September 2009 were studied prospectively. Ethics approval was obtained (MUMS-84386). These subjects were randomly allocated into 4 groups 1. sodium bicarbonate (S). 2. magnesium sulphate (M) 3. both (B) and 4. none (N). All cases received fluids and atropine as well as diazepam if needed. Results: 27 S, 25 M, 27 B and 26 N subjects were studied. Age, gender, addiction and severity of poisoning were not significantly different in these four groups. There were no significant differences in atropine administration, mechanical ventilation, ICU admission and deaths in these groups. Magnesium sulphate significantly reduced mean duration of admission ($P = 0.041$), diazepam administration ($P = 0.015$) and seizure ($P = 0.003$). Conclusion: This study does not support previous findings in regard to beneficial effects of sodium bicarbonate, which might be due to limited power of the study. It suggests that magnesium sulphate may prevent seizures, reduce the need for diazepam administration and decrease duration of admission. Further studies in this regard are warranted.

Pawar, K. S., R. R. Bhoite, et al. (2006). "Continuous pralidoxime infusion versus repeated bolus injection to treat organophosphorus pesticide poisoning: a randomised controlled trial." *Lancet* **368**(9553): 2136-2141.

BACKGROUND: The role of oximes for the treatment of organophosphorus pesticide poisoning has not been conclusively established. We aimed to assess the effectiveness of a constant pralidoxime infusion compared with repeated bolus doses to treat patients with moderately severe poisoning from organophosphorus pesticides. METHODS: 200 patients were recruited to our single-centre, open randomised controlled trial after moderately severe poisoning by anticholinesterase pesticide. All were given a 2 g loading dose of pralidoxime over 30 min. Patients were then randomly assigned to control and study groups. Controls were given a bolus dose of 1 g pralidoxime over 1 h every 4 h for 48 h. The study group had a constant infusion of 1 g over an hour every hour for 48 h. Thereafter, all patients were given 1 g every 4 h

until they could be weaned from ventilators. Analysis was by intention to treat. Primary outcome measures were median atropine dose needed within 24 h, proportion of patients who needed intubation, and number of days on ventilation. The study is registered at <http://www.clinicaltrials.gov> with the identifier NCT00333944. FINDINGS: 100 patients were assigned the high-dose regimen, and 100 the control regimen. There were no drop-outs. Patients receiving the high-dose pralidoxime regimen required less atropine during the first 24 h than controls (median 6 mg vs 30 mg; difference 24 mg [95% CI 24-26, $p < 0.0001$]). 88 (88%) and 64 (64%) of controls and high-dose patients, respectively, needed intubation during admission to hospital (relative risk=0.72, 0.62-0.86, $p = 0.0001$). Control patients required ventilatory support for longer (median 10 days vs 5 days; difference 5 days [5-6, $p < 0.0001$]). INTERPRETATION: A high-dose regimen of pralidoxime, consisting of a constant infusion of 1 g/h for 48 h after a 2 g loading dose, reduces morbidity and mortality in moderately severe cases of acute organophosphorus-pesticide poisoning.

Pearson, M., F. Konradsen, et al. (2011). "A community-based cluster randomised trial of safe storage to reduce pesticide self-poisoning in rural Sri Lanka: study protocol." *BMC Public Health* **11**: 879.

BACKGROUND: The WHO recognises pesticide poisoning to be the single most important means of suicide globally. Pesticide self-poisoning is a major public health and clinical problem in rural Asia, where it has led to case fatality ratios 20-30 times higher than self-poisoning in the developed world. One approach to reducing access to pesticides is for households to store pesticides in lockable "safe-storage" containers. However, before this approach can be promoted, evidence is required on its effectiveness and safety. METHODS/DESIGN: A community-based cluster randomised controlled trial has been set up in 44,000 households in the North Central Province, Sri Lanka. A census is being performed, collecting baseline demographic data, socio-economic status, pesticide usage, self-harm and alcohol. Participating villages are then randomised and eligible households in the intervention arm given a lockable safe storage container for agrochemicals. The primary outcome will be incidence of pesticide self-poisoning over three years amongst individuals aged 14 years and over. 217,944 person years of follow-up are required in each arm to detect a 33% reduction in pesticide self-poisoning with 80% power at the 5% significance level. Secondary outcomes will include the incidence of all pesticide poisoning and total self-harm. DISCUSSION: This paper describes a large effectiveness study of a community intervention to reduce the burden of intentional poisoning in rural Sri Lanka. The study builds on a strong partnership between provincial health services, local and international researchers, and local communities. We discuss issues in relation to randomisation and contamination, engaging control villages, the intervention, and strategies to improve adherence.

Pearson, M., A. B. Zwi, et al. (2014). "Taking stock -- what is known about suicide in Sri Lanka: a systematic review of diverse literature." *Crisis* **35**(2): 90-101.

BACKGROUND: Suicide is and has been a major public health problem in Sri Lanka and has generated a wide range of literature. AIMS: This review

aimed to systematically appraise what is known about suicide in Sri Lanka. The patterns and content of articles were examined and recommendations for further research proposed. **METHOD:** The paper describes the systematic search, retrieval, and quality assessment of studies. Thematic analysis techniques were applied to the full text of the articles to explore the range and extent of issues covered. **RESULTS:** Local authors generated a large body of evidence of the problem in early studies. The importance of the method of suicide, suicidal intention, and the high incidence of suicide were identified as key foci for publications. Neglected areas have been policy and health service research, gender analysis, and contextual issues. **CONCLUSION:** The literature reviewed has produced a broad understanding of the clinical factors, size of the problem, and social aspects. However, there remains limited evidence of prevention, risk factors, health services, and policy. A wide range of solutions have been proposed, but only regulation of pesticides and improved medical management proved to be effective to date.

Pruss-Ustun, A., C. Vickers, et al. (2011). "Knowns and unknowns on burden of disease due to chemicals: a systematic review." *Environ Health* **10**: 9.

BACKGROUND: Continuous exposure to many chemicals, including through air, water, food, or other media and products results in health impacts which have been well assessed, however little is known about the total disease burden related to chemicals. This is important to know for overall policy actions and priorities. In this article the known burden related to selected chemicals or their mixtures, main data gaps, and the link to public health policy are reviewed. **METHODS:** A systematic review of the literature for global burden of disease estimates from chemicals was conducted. Global disease due to chemicals was estimated using standard methodology of the Global Burden of Disease. **RESULTS:** In total, 4.9 million deaths (8.3% of total) and 86 million Disability-Adjusted Life Years (DALYs) (5.7% of total) were attributable to environmental exposure and management of selected chemicals in 2004. The largest contributors include indoor smoke from solid fuel use, outdoor air pollution and second-hand smoke, with 2.0, 1.2 and 0.6 million deaths annually. These are followed by occupational particulates, chemicals involved in acute poisonings, and pesticides involved in self-poisonings, with 375,000, 240,000 and 186,000 annual deaths, respectively. **CONCLUSIONS:** The known burden due to chemicals is considerable. This information supports decision-making in programmes having a role to play in reducing human exposure to toxic chemicals. These figures present only a number of chemicals for which data are available, therefore, they are more likely an underestimate of the actual burden. Chemicals with known health effects, such as dioxins, cadmium, mercury or chronic exposure to pesticides could not be included in this article due to incomplete data and information. Effective public health interventions are known to manage chemicals and limit their public health impacts and should be implemented at national and international levels.

Rajapakse, T., K. M. Griffiths, et al. (2013). "Characteristics of non-fatal self-poisoning in Sri Lanka: a systematic review." *BMC Public Health* **13**: 331.

BACKGROUND: The rate of non-fatal self-poisoning in Sri Lanka has increased in recent years, with associated morbidity and economic cost to

the country. This review examines the published literature for the characteristics and factors associated with non-fatal self-poisoning in Sri Lanka. **METHODS:** Electronic searches were conducted in Psychinfo, Proquest, Medline and Cochrane databases from inception to October 2011. **RESULTS:** 26 publications (representing 23 studies) were eligible to be included in the review. A majority of studies reported non-fatal self-poisoning to be more common among males, with a peak age range of 10-30 years. Pesticide ingestion was the most commonly used method of non-fatal self-poisoning. However three studies conducted within the last ten years, in urban areas of the country, reported non-fatal self-poisoning by medicinal overdose to be more common, and also reported non-fatal self-poisoning to be more common among females. Interpersonal conflict was the most commonly reported short-term stressor associated with self-poisoning. Alcohol misuse was reported among males who self-poisoned, and data regarding other psychiatric morbidity was limited. **CONCLUSIONS:** The findings indicate that pesticide ingestion is the commonest method of non-fatal self-poisoning in Sri Lanka, and it is more common among young males, similar to other Asian countries. However there appears to be an emerging pattern of increasing medicinal overdoses, paralleled by a gender shift towards increased female non-fatal self-poisoning in urban areas. Many non-fatal self-poisoning attempts appear to occur in the context of acute interpersonal stress, with short premeditation, and associated with alcohol misuse in males. Similar to other Asian countries, strategies to reduce non-fatal self-poisoning in Sri Lanka require integrated intervention programs with several key aspects, including culturally appropriate interventions to develop interpersonal skills in young people, community based programs to reduce alcohol misuse, and screening for and specific management of those at high risk of repetition following an attempt of self-poisoning.

Roberts, D. and N. A. Buckley (2005). "Alkalinisation for organophosphorus pesticide poisoning." *Cochrane Database Syst Rev*(1): CD004897.

BACKGROUND: Poisoning with organophosphorus pesticides (OPs) is an important cause of morbidity and mortality in all parts of the world, particularly developing countries. The case-fatality ratio for pesticide intentional self-poisoning is around 10-20% even when the standard antidotes (atropine, oximes and benzodiazepines) are used. Alternative treatments have been trialled in an attempt to improve outcomes from acute OP poisoning, one of which is plasma alkalinisation. Animal and preliminary human research has suggested benefit from plasma alkalinisation with sodium bicarbonate (NaHCO₃) as a treatment for acute OP poisoning. **OBJECTIVES:** To determine the efficacy of alkalinisation, in particular NaHCO₃, for the treatment of acute OP poisoning. **SEARCH STRATEGY:** We searched MEDLINE (1966-2004), EMBASE (1980-2004), the Controlled Trials Register of the Cochrane Collaboration, Current Awareness in Clinical Toxicology, Info Trac, <http://www.google.com.au>, and Science Citation Index of studies identified by the previous searches. We also manually reviewed the bibliographies of identified articles and personally contacted experts in the field. **SELECTION CRITERIA:** Randomised controlled trials and controlled clinical trials of symptomatic patients following acute OP poisoning treated with alkalinisation. The quality of studies and eligibility for inclusion

was assessed using criteria by Jadad and Schulz. DATA COLLECTION AND ANALYSIS: Studies were identified and both authors independently extracted data which was recorded on a pre-designed form. Study design, including the method of randomisation, participant characteristics, type of intervention and outcomes were recorded. Outcomes were discussed, but unfortunately specific analyses could not be performed, given the poor quality of the studies identified. MAIN RESULTS: Five studies were identified but none satisfied inclusion criteria. NaHCO₃ was used in each of these to induce alkalinisation. Two studies were uncontrolled, two studies were historically controlled and one study was randomised but poorly concealed. Marked heterogeneity between subjects and treatments was noted - for example, a different regimen of NaHCO₃ was used in each study. While there may have been a trend towards improved outcomes (lower total dose of atropine and shorter length of stay), these were not statistically significant. AUTHORS' CONCLUSIONS: There is insufficient evidence to support the routine use of plasma alkalinisation for treatment of OP poisoning. Further research is required to determine the method of alkalinisation that will optimise outcomes, and the regimen which will produce the target arterial pH of 7.50 (range 7.45-7.55). This should be followed by a well-designed randomised controlled trial to determine efficacy.

Shadnia, S., S. Ashrafiand, et al. (2011). "N-acetylcysteine a novel treatment for acute human organophosphate poisoning." International Journal of Pharmacology **7** (6): 732-735.

Since oxidative stress markers are increased in Organophosphates (OPs) toxicity, the efficacy of the antioxidant N-acetyl-L-cysteine (NAC) as an adjunct therapy to atropine and pralidoxime for acute OPs toxicity was evaluated. Twenty-four adult subjects with acute OP toxicity were included in a randomized single blind controlled trial on the use of intravenous NAC. Among included subjects, twelve were randomized to receive NAC and the rest did not receive NAC. The results showed that the need for atropine but not pralidoxime was reduced in NAC group. The duration of hospitalization was reduced in the NAC group. Addition of NAC to current treatment protocol of acute OPs poisoning is recommended. 2011 Asian Network for Scientific Information.

Vijayakumar, L., L. Jeyaseelan, et al. (2013). "A central storage facility to reduce pesticide suicides--a feasibility study from India." BMC Public Health **13**: 850.

BACKGROUND: Pesticide suicides are considered the single most important means of suicide worldwide. Centralized pesticide storage facilities have the possible advantage of delaying access to pesticides thereby reducing suicides. We undertook this study to examine the feasibility and acceptability of a centralized pesticide storage facility as a preventive intervention strategy in reducing pesticide suicides. METHODS: A community randomized controlled feasibility study using a mixed methods approach involving a household survey; focus group discussions (FGDs) and surveillance were undertaken. The study was carried out in a district in southern India. Eight villages that engaged in floriculture were identified. Using the lottery method two were randomized to be the intervention sites and two villages constituted the control site. Two centralized storage facilities were constructed with local

involvement and lockable storage boxes were constructed. The household survey conducted at baseline and one and a half years later documented information on sociodemographic data, pesticide usage, storage and suicides. RESULTS: At baseline 4446 individuals (1097 households) in the intervention and 3307 individuals (782 households) in the control sites were recruited while at follow up there were 4308 individuals (1063 households) in the intervention and 2673 individuals (632 households) in the control sites. There were differences in baseline characteristics and imbalances in the prevalence of suicides between intervention and control sites as this was a small feasibility study. The results from the FGDs revealed that most participants found the storage facility to be both useful and acceptable. In addition to protecting against wastage, they felt that it had also helped prevent pesticide suicides as the pesticides stored here were not as easily and readily accessible. The primary analyses were done on an Intention to Treat basis. Following the intervention, the differences between sites in changes in combined, completed and attempted suicide rates per 100,000 person-years were 295 (95% CI: 154.7, 434.8; $p < 0.001$) for pesticide suicide and 339 (95% CI: 165.3, 513.2, $p < 0.001$) for suicide of all methods. CONCLUSIONS: Suicide by pesticides poisoning is a major public health problem and needs innovative interventions to address it. This study, the first of its kind in the world, examined the feasibility of a central storage facility as a means of limiting access to pesticides and, has provided preliminary results on its usefulness. These results need to be interpreted with caution in view of the imbalances between sites. The facility was found to be acceptable, thereby underscoring the need for larger studies for a longer duration. TRIAL REGISTRATION ISRCTN: ISRCTN04912407.