Oximes for acute organophosphate pesticide poisoning (Review)

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[Intervention Review]

Oximes for acute organophosphate pesticide poisoning

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ABSTRACT

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 reactivate inhibited acetylcholinesterase. The clinical usefulness of oximes, such as pralidoxime and obidoxime, has been challenged over the past 20 years by physicians in many parts of the world.

Objectives

To quantify the effectiveness and safety of the administration of oximes in acute organophosphorus pesticide-poisoned patients.

Search methods

We searched both English and Chinese databases: Cochrane Injuries Group Specialised Register, Cochrane Central Register of Controlled Trials (*The Cochrane Library*), MEDLINE (Ovid SP), EMBASE (Ovid SP), ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED), ISI Web of Science: Conference Proceedings Citation Index-Science (CPCI-S) and the Chinese language databases CNKI and WANGFANG. All searches were run in September 2009.

Selection criteria

Articles that could possibly be RCTs were retrieved to determine if they were randomised.

Data collection and analysis

The published methodology of three RCTs was not clear. We contacted the principal authors of these, but did not obtain further information.

Main results

Seven pralidoxime RCTs were found. Three RCTs including 366 patients studied pralidoxime vs placebo and four RCTs including 479 patients compared two or more different doses. These trials found quite disparate results with treatment effects ranging from benefit to harm. However, many studies did not take into account several issues important for outcomes. In particular, baseline characteristics were not balanced, oxime doses varied widely, there were substantial delays to treatment, and the type of organophosphate was not taken into account. Only one RCT compared the World Health Organization (WHO) recommended doses with placebo. This trial showed

no clinical benefits and a trend towards harm in all sub-groups, despite clear evidence that these doses reactivated acetylcholinesterase in the blood.

Authors' conclusions

Current evidence is insufficient to indicate whether oximes are harmful or beneficial. The WHO recommended regimen (30 mg/kg pralidoxime chloride bolus followed by 8 mg/kg/hr infusion) is not supported. Further RCTs are required to examine other strategies and regimens. There are many theoretical and practical reasons why oximes may not be useful, particularly for late presentations of dimethyl OP and those with a large excess of OP that simply re-inhibits reactivated enzymes. Future studies should screen for patient sub-groups that may benefit and may need flexible dosing strategies as clinical effectiveness and doses may depend on the type of OP.

PLAIN LANGUAGE SUMMARY

No evidence that oximes are a useful treatment for organophosphate pesticide poisoning

Many thousands of people die every year because of poisoning by organophosphate pesticides. Most of the deaths are in developing countries. Drugs known as oximes are used as part of the standard recommended treatment, even though many doctors have said that they don't seem to have any benefit. This research has produced mixed evidence. Many of the studies had substantial limitations. Generally, the studies done to date do not support the routine use of oximes, however, they cannot exclude that there would be some doses or situations where a benefit would occur. The reviewers found that not enough research has been done to see whether oximes are actually effective or to define the doses that are more likely to be helpful. More research is needed before any firm conclusions can be drawn.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Oxime compared to placebo for acute organophosphate pesticide poisoning

Patient or population: patients with acute organophosphate pesticide poisoning
Settings:
Intervention: Oxime
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	placebo	Oxime				
Deaths	Study population		OR 2.68 (0.93 to 7.72)	366 (3 studies)	⊕◯◯◯ very low[1,2,3]	
	122 per 1000	271 per 1000 (114 to 518)				
	Medium risk population					
	91 per 1000	212 per 1000 (85 to 436)				
Intermediate syndrome	Study population		OR 3.4 (1.62 to 7.17)	110 (1 study)	⊕◯◯◯ very low[4,5,6,7]	
	345 per 1000	642 per 1000 (460 to 791)				
	Medium risk population					
	346 per 1000	643 per 1000 (462 to 791)				
Ventilated	Study population		OR 2 (0.81 to 4.95)	366 (3 studies)	⊕◯◯◯ very low[1,2,3,8]	

	278 per 1000	**435 per 1000** (238 to 656)
	Medium risk population	
	364 per 1000	**534 per 1000** (317 to 739)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Two modest sized RCTs plus one very small RCT. Two studies have high risk of bias. The largest and better quality study was stopped early.
[2] Confidence intervals indicate results are consistent with both a substantial risk and no effect. Total number of events is much less than 300. Further imprecision added by lack of information on whether studies have used the optimal dosing strategy.
[3] There are too few trials to make an informed judgement about the risk of publication bias
[4] Small study with substantial risk of bias. Low dose of PAM given may lack efficacy.
[5] Outcome/diagnosis may be subjective
[6] Only one study contributing - while it is a statistically significant result, the confidence interval is wide.
[7] Only one unblinded study provided information about this outcome.
[8] The largest best quality is most consistent with no difference, point estimates for the other two do not lie within the CI of the best quality study

BACKGROUND

Acute poisoning with organophosphorus pesticides causes severe toxicity. They act primarily by inhibiting an enzyme (acetylcholinesterase) in the nervous system. Oximes are drugs designed to reactivate this enzyme.

Deliberate self-poisoning has reached epidemic proportions in parts of the developing world where the toxicity of available poisons and sparse medical facilities ensure a high fatality rate (Murray 1996; Eddleston 2000). Many deaths are due to organophosphorus pesticides (OP) and occur in the young economically active age group (Singh 1997; Eddleston 1998; Van der Hoek 1998; Eddleston 2003). Case fatality of >20% is commonly reported and the World Health Organization (WHO) estimated that 200,000 people die each year from pesticide poisoning (WHO 1990). Even higher figures have been estimated based on more recent data (Gunnell 2007). Unfortunately, the widespread use of OP pesticides in the developing world's agricultural communities will make reduction of deaths by primary prevention a difficult task.

OP pesticides inhibit acetylcholinesterase (AChE) at the muscarinic and nicotinic synapses by depositing a phosphoryl group at the enzyme's active site. This results in an accumulation of acetylcholine and uncontrolled activation of cholinergic synapses. Standard therapy involves attempts to reduce absorption with gastric lavage and/or activated charcoal, plus administration of atropine and oxime to counter the effects of absorbed pesticide (Ballantyne 1992; Johnson 2000; Eddleston 2008). The use of high doses of atropine is well established, the use of oximes more controversial.

Oximes reactivate acetylcholinesterase by removing the phosphoryl group. Pralidoxime is the oxime most often used worldwide and occurs in four forms: pralidoxime chloride (2-PAM; molecular weight 173; used worldwide), pralidoxime mesylate (P2S; MW 232; used in the UK), pralidoxime metilsulfate (MW 248) and pralidoxime iodide (MW 264; used in Japan, India & Australia) (Eyer 2008). The great majority of its effects are on the peripheral nervous system since its lipid solubility is low and entry into the CNS limited. Atropine works at muscarinic synapses, competitively antagonising the accumulated acetylcholine. The main therapeutic effect of pralidoxime is predicted to be recovery of neuromuscular transmission at nicotinic synapses.

In vitro experiments have shown that oximes are effective reactivators of human AChE inhibited by OP compounds (Worek 1996). In some situations, however, reactivation of inhibited AChE by oximes will likely be absent or limited, for example where there is:

1. poor affinity for the particular OP-AChE complex
2. insufficient dose or duration of treatment
3. persistence of the OP within the patient and therefore rapid re-inhibition of newly reactivated enzyme *and*
4. ageing of the inhibited AChE (Willems 1993; Thiermann 1997; Worek 1997; Johnson 2000; Eyer 2009).

In 1961, Sundwall reported that the minimum effective plasma concentration of P2S was 4 mg/L in cats poisoned with a quaternary analogue of the nerve agent sarin (Sundwall 1961). This result has since been uncritically extrapolated to all oxime and OP interactions. It has now become clear, however, that the degree of reactivation is dependent on the specific identity and concentrations of both the oxime and OP (Willems 1993; Worek 1996; Johnson 2000). For example, most OP pesticides can be classified as compounds that form either a dimethylphosphoryl- or a diethylphosphoryl-AChE complex. In vitro studies have shown that while seven times as much pralidoxime as obidoxime is required for reactivation of dimethyl-OP inhibited AChE, diethyl-OPs require 20 times more pralidoxime than obidoxime (Thiermann 1999). Both reactivation and ageing are significantly slower for diethyl-OP inhibited AChEs than the dimethyl analogue. In addition, OP are a highly variable toxicological class in many other respects. This is reflected both in very large differences in their case-fatality (Eddleston 2005, Dawson 2010), and also in very marked differences in the timecourse of AChE inhibition and resulting spectrum of adverse effects (Eddleston 2005; Eddleston 2009a). Thus in evaluating the evidence, particularly where it appears to be conflicting, it is necessary to consider the possibility that any effects of oximes are not consistent across all OPs.

The 'ageing' of inhibited AChE is particularly important since aged enzyme cannot be reactivated by oximes. Ageing refers to a process whereby phosphorylated acetylcholinesterase may lose an alkyl side chain non-enzymatically, leaving a hydroxyl group in its place. Regeneration is then no longer possible. The therapeutic window for oximes is, therefore, very much determined by the rate of ageing. The half-life of ageing of dimethylphosphorylated and diethlyphosphorylated AChE, as determined in isolated human red cells in vitro, is 3.7 hours and 33 hours, respectively (Worek 1997; Worek 1999) and the therapeutic window therefore (taken as four times the half-life of ageing) is a maximum of 13 or 132 hours, respectively (Bismuth 1992; Worek 1997). For some other OP classes ageing may be much quicker than this and therapeutic window closed at the time the patient arrives to hospital (Eddleston 2009a). Clinical data of OP-poisoned patients treated with obidoxime illustrate the importance of poison load, time elapsing between poisoning and oxime administration, and influence of the poison type (in particular dimethyl versus diethyl) on the effectiveness of reactivation of erythrocyte AChE in vivo (Thiermann 2009).

However, clinical experience in the developing world has led to doubt about the clinical relevance of oximes for any form of OP poisoning (Nalin 1973; Ganendran 1976; du Toit 1981; Delilkan 1984; de Silva 1992; Singh 1995; Sungur 2001). In particular, Senanayake's group, using a historical control design, reported no difference in outcome in Sri Lanka when pralidoxime was unavailable in their hospital (de Silva 1992). They argued that pralidoxime was of no clinical benefit and should not be used. Propo-

nents of oximes responded that these physicians were using too low a dose and that a loading dose of at least 30 mg/kg followed by an infusion of >8 mg/kg/hr was required for clinical benefit (Johnson 1992; Vale 1996; Johnson 2000).

OBJECTIVES

To quantify the effectiveness and safety of the administration of oximes in acute organophosphorus pesticide-poisoned patients.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised clinical trials.

Types of participants

Acute OP poisoning (deliberate or accidental). This we defined as patients presenting with typical clinical effects due to and following shortly after a single exposure to OP.

Types of interventions

Any oxime (pralidoxime, obidoxime, HI-6, etc).

Types of outcome measures

Primary outcomes

- Death.

Secondary outcomes

- Pneumonia, intermediate syndrome (onset of progressive weakness after 24−96 hours when acute cholinergic symptoms have resolved), need for ventilation, duration of ventilation, significant persistent neurological injury (motor/sensory neuropathy, Parkinsonism, hemiparesis, etc.).

Search methods for identification of studies

Searches were not restricted by date, language or publication status

Electronic searches

We searched the following electronic databases;

- Cochrane Injuries Group Specialised Register (searched 10 Sept 2009);
- Cochrane Central Register of Controlled Trials 2009, Issue 3 (*The Cochrane Library*)
- MEDLINE (Ovid SP) 1950 to September Week 1 2009;
- EMBASE (Ovid SP) 1980 to August 2009 (Week 36);
- 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
- PubMed [www.ncbi.nlm.nih.gov/sites/entrez/] (searched 10 Sept 2009) (added to PubMed in the last 90 days).

All search strategies are reported in full Appendix 1.

Searching other resources

Other searches included;

- www.google.com and www.Clinicaltrials.gov
- CNKI www.cnki.net and WANGFANG www.wangfang.com for Chinese articles
- Reference lists of previously published reviews (e.g. Peter 2008; Eyer 2003) and eligible trials to identify further relevant studies that were not previously picked up by the database searches
- Contacting experts in the field to identify further published and unpublished studies.

All search strategies are reported in full in Appendix 2.

Data collection and analysis

The Injuries Group Trials Search Co-ordinator ran the searches and collated the search results before passing them on to the review authors (ME & JR) for screening. All randomised controlled trials involving acute poisoning with organophosphorus compounds treated with oximes, regardless of severity, with adequate or unclear allocation concealment were examined. Two authors (ME & JR) independently completed the GRADE evaluation and summary of findings table with any differences resolved by a third reviewer (NB).

In total, we found five published RCTs in English (Characteristics of included studies). There were also conference abstracts describing small clinical studies, where the methodology is unclear (Dadan 1998; Duval 1991). We think these very small studies are very unlikely to be RCTs and were excluded after attempts to contact the authors failed to yield a response to clarify the methodology. All identified studies assessed pralidoxime; clinical trials of obidoxime or other oximes have not been reported.

For this 2010 update, two reviewers (JR & MB) independently extracted from each trial information on the number of randomised

patients, types of participants, the dose and duration of the intervention, and the primary and secondary outcomes of the trial. YL performed the same procedure on the Chinese studies identified through Chinese language database searches. A pooled odds ratio (OR) for the presence of death, intermediate syndrome and pneumonia were calculated using a random effects model if more than one adequate quality trial included the same comparison (e.g. pralidoxime vs placebo) and outcome. A random effects model was chosen on the basis that the settings, types of OP ingested and doses of oxime vary extremely widely so a fixed effect model cannot be justified. Subgroup analysis based on type of organophosphorus compound (dimethyl vs diethyl) and time to treatment was to be included if possible.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Samuel 1995

The first trial in 72 patients admitted to an Intensive Care Unit was carried out between August 1991 and November 1992 at the Christian Medical College in Vellore, India. There was no untreated control group. A 1-g bolus of pralidoxime (termed 'low-dose') was compared with 12 g given as a reducing infusion over four days without a loading dose (termed 'high-dose').

Cherian 1997

The dates of this second trial from the Vellore group are not given in either publication. Following on from Samuel 1995, it compared 'high-dose' pralidoxime (i.e. a total of 12 g by continuous infusion over 3 days without loading dose) with placebo saline infusion in 110 patients. Although the published details are incomplete, it appears that a different dosage regimen to that of Samuel 1995 was used: 12 g over three days.

Cherian 2005

This third study from Vellore largely explored the biochemical effects of pralidoxime on butylcholinesterase (BuChE) and the correlations of BuChE activity with severity. Just 21 patients were included and the dose of pralidoxime in the treatment arm varied (either 4g/day or 12g /day was given) based on the severity of poisoning. While OP bind to and inhibit BuChE in plasma and it is a widely available biomarker of exposure, the inhibition of this enzyme itself is not believed to be a causal factor in any clinical features. Further, different OP have widely varying preferences for inhibiting BuChE vs. AChE so the OP ingested must be known for it to be used as a marker of severity (Eddleston 2008a). Thus, even the results on BuChE are difficult to interpret.

Pawar 2006

This study was conducted in a private hospital ICU in India. Unusually, patients purchased their own pralidoxime for the RCT from outside local pharmacies. This was assumed to be pralidoxime iodide although there obviously could not be effective control over the trial product or blinding. 200 patients with moderate OP poisoning were enrolled. All patients received a 2 gram loading dose of pralidoxime before randomisation to "low dose" (standard treatment control) and "high dose" groups. This standard "low dose" (6g/day) was actually substantially higher than the highest dose in the first two Vellore studies. The high dose was higher than previously recommended by the WHO: 1g/hr for the first 48h. Both groups then continued on standard treatment (6g/day) until weaned from ventilation. The overall mortality for OP poisoning admitted to ICU was remarkably low, but particularly so in the high dose group (1%). The patients had presented early to hospital (median 2 hours). Those who were most severely ill on presentation were excluded. There was a very high level of supportive care (e.g. all were admitted to ICU and 66% of these moderately-severely poisoned patients were intubated at baseline). No mechanistic data were available to demonstrate whether the higher dose of pralidoxime had a greater effect on neuromuscular function or acetylcholinesterase activity.

Eddleston 2009

This Wellcome Trust funded study was conducted in two hospitals in Sri Lanka. A high fixed regimen based on WHO guidelines (2g bolus then 500mg/hr for up to 7 days) was used in all patients in the treatment arm. Controls received a placebo infusion. As well as the clinical outcomes (discussed below), the pralidoxime concentrations achieved and the reactivation of red blood cell acetylcholinesterase (RBC-AChE) were measured to document that apparently effective doses were given. The trial was originally planned with a sample size of 1500. However, delays in starting the study due to a global shortage of pralidoxime after Sept 11 2001, and a substantial fall off in recruitment after the Pawar 2006 study was published, lead to it being prematurely terminated after just 235 patients were enrolled. Measures of RBC-AChE activity indicated the regimen was effective in reactivating AChE particularly for diethyl-OP. The mean pralidoxime concentrations achieved were in the target range predicted, however, there was substantial variability.

Zhu 2006

This very small RCT enrolled 24 patients presenting to an emergency medicine service in China compared two regimens of pralidoxime, with one arm being given roughly double the dose of the other arm and both being reduced over time.

Gu 2008

This RCT enrolled 187 patients also from an emergency medicine service in China. The report is of a very complex three arm trial with each arm having two different flexible dosing strategies (for moderate and severely poisoned patients). The means of measuring severity was not explicit. Further not only were three different dosing strategies being compared but also different routes of

administration (IV vs. IM). The randomised ratio appears to be highly unusual (roughly 3:3:4) and was stated to be based on "Arabic numbers".

Overall comments on included studies

These last two trials were only reported in Chinese and this raised many difficulties in resolving what methodology had been used. For example, it is not clear the Chinese characters denoting random assignment have the exact same meaning as the English word and there are not sufficient details of randomisation recorded to be certain that a truly random method had been used for assignment. No two RCTs examined the same dose comparison. Pralidoxime comes in different salts (Bismuth 1992) and thus for ease of comparison we have summarised the pralidoxime cation (active drug) doses in the studies in Table 1.

Selected other comparative studies with roughly equal numbers in the two arms (excluded as not stated to be randomised):

Abdollahi 1995

A trial of pralidoxime carried out in 34 patients in Tehran, Iran, during the early 1990s. Seventeen patients received atropine alone while 17 received 600−800 mg pralidoxime every 4−8h for four days in addition to atropine. The pralidoxime dose was based on the patient's condition.

Dadan 1998

This study has been published in abstract format only. Twenty OP-poisoned patients were included in this trial of two vials or four vials of pralidoxime iodide. It seems unlikely this is a randomised study but no response was received from the author when we attempted to clarify this.

de Silva 1992

This study was a retrospective comparison of outcomes from two cohorts when pralidoxime was and wasn't available in Sri Lanka. 21 patients with moderate to severe OP poisoning treated with just atropine were compared to 24 patients treated with atropine plus pralidoxime. There were no differences in mortality, length of stay, need for ventilation or ICU and the authors called for a re-evaluation of the use of cholinesterase reactivators.

Duval 1991

This is a retrospective comparison of two cohorts of 31 patients. One cohort received 200 mg pralidoxime every 4 hours and the others received no oxime treatment. There were no differences in mortality, need for ventilation or atropine use and the authors suggested randomised clinical trials are needed to confirm these results.

Li 2003

This study in 84 patients with severe acute OP poisoning presenting to an emergency medicine service in Sichuan China was not described as randomised. The OPs ingested were dimethoate (28), methamidophos (26), parathion (16), and dichlorvos (14). All patients were treated with pralidoxime chloride. Half received 1g IV loading dose and 500mg/hr until the AChE was > 60% and the other half 1-1.5g iv, repeated once 30mins later and then 500mg IV for 6 hrs. 14/42 patients died with the first regimen and 7/42 with the second. No other outcomes were reported.

Li 2009

This study in 67 patients with severe acute OP poisoning presenting to an emergency medicine service in Henan China was not described as randomised. The OPs ingested were not reported. All patients were treated with pralidoxime chloride. Half received 0.75-2.5g pralidoxime infused in 30min;1g/hr for 48hrs; then 1g q4h for 72hrs (if still unwell). The other half received 1.5-2.5g pralidoxime IM; then 1g q 4hr for up to 72hrs. All the outcomes were better with the first regimen (deaths 1/34 vs. 5/33; intermediate syndrome 0/34 vs. 8/33; intubations 3/34 vs. 9/33; 'normal AChE' at 7 days 76% vs. 21%).

Shivakumar 2006

This is a retrospective study only reported in a long item of correspondence comparing outcomes in 58 ventilated patients who received high dose (>4g total) vs lower doses. 81 mild cases were excluded from analysis as were 26 patients who died simply because a ventilator was not available. The authors claimed better survival in those treated with high doses (83.7% vs 53.3%) and less intermediate syndrome (49% vs 72%). They called for RCTs further evaluating higher doses of pralidoxime.

Zheng 2000

This is a retrospective study published in Chinese with an English abstract. Seventy-six cases of severe OP poisoning were compared in a post-hoc analysis. 30 had received a higher dose (10-26 g/day) and 46 a lower dose (3.3-8.6 g/day). The OPs ingested were dichlorvos (46); dimethoate (22) and parathion (8). The authors claimed better outcomes with the higher dose, including lower mortality (deaths 7/30 (27%) vs. 36/46 (78%)).

Risk of bias in included studies

For the two larger Vellore studies (Samuel 1995 and Cherian 1997); we wrote to the authors to clarify the methodology used in their trials in line with the CONSORT statement (Moher 2001) but received no response. Allocation concealment and method of randomisation are not apparent from the published trials. Both RCTs used a small fixed block size of four, which may have allowed subversion of randomisation through failure of allocation concealment for some patients (Schulz 2002). A placebo was used in both trials but it is not stated who was blinded to the intervention.

Pawar 2006 also used a small fixed block size of four which may have allowed subversion of randomisation through failure of allocation concealment for some patients (Schulz 2002). A placebo was used but it is not stated who was blinded to the allocation. Patients' families had to purchase the pralidoxime so blinding must have been limited.

The main risk of bias with Eddleston 2009 arises in the earlier than planned termination of this study. This was done in the light of poor recruitment following publication of the Pawar study. It is possible that stopping early may have resulted in an exaggerated

estimate of harm. However, in other respects this trial had a more robust design than previous studies with stratified randomisation, allocation concealment, double blind design and verifiable clinical and biochemical outcomes.

It was quite hard to judge the risk of bias in the two Chinese studies as the reporting did not disclose many important aspects of trial design. Not surprisingly, reference to CONSORT guidelines when reporting these clinical trials in China did not appear to have occurred. We hope the recent Chinese translation of these guidelines (Moher 2010) may make this task easier in the next version of this review.

Only one study (Eddleston 2009) had a clearly defined sample size calculation and although this study was the largest it still fell well short of the target. Thus all studies may be affected by bias due to premature stopping which may lead to exaggerated estimates of the magnitude of both benefits and harms (Bassler 2010).

Effects of interventions

See: **Summary of findings for the main comparison** Oxime compared to placebo for acute organophosphate pesticide poisoning; **Summary of findings 2** Higher dose compared to lower dose for acute organophosphate pesticide poisoning

Samuel 1995

This RCT reported a higher case-fatality (22% vs. 14%; OR 1.77 (95% CI 0.52-6.0)), increased requirement for ventilation (67% vs. 47%; OR 2.04 (95% CI 0.78-5.3)) and increased rate of Intermediate syndrome (56% vs. 36%; OR 2.2 (95% CI 0.86-5.7)) amongst patients who received the pralidoxime infusion (12 g given as a reducing infusion over four days) compared to those who received a single bolus dose (1 g STAT IV). There was no substantial difference in the duration of ventilation (mean (SD) 181 (125) vs 164 (115) hours, P=0.70).

The authors argued that 'high-dose' pralidoxime was therefore "associated with a worse outcome" and should have "no role in the routine management of patients with OP poisoning".

Cherian 1997

In this RCT, pralidoxime (12g over three days (estimated 3.7 mg/kg/hr for a 45 kg patient)) was associated with a significantly higher risk of death (29% vs. 5%; OR 7.1 (95% CI 1.9-26.0)), requirement for ventilation (67% vs. 40%; OR 3.1 (95% CI 1.4-6.7)) and increased rate of Intermediate syndrome (65% vs. 35%; OR 3.4 (95% CI 1.6-7.2)). There was no substantial difference in the duration of ventilation (mean 7.6 days (SD 6.3) for treatment group vs. 8.4 days (SD7.3) p=0.43). Infections were also higher in the treatment group (45% vs 25%) but pneumonia was not specifically reported.

The authors concluded that 2PAM "has no role in the management of patients with organophosphorus poisoning and ... does more harm than good".

Cherian 2005

In this very small RCT (n=21), the primary aims were to look at the effects of treatment on the biomarker of BuChE activity and the correlation of BuChE activity with outcomes. There was 1 death in each arm of the trial; 7/10 treated vs 4/11 controls were ventilated and the duration of ventilation was longer in the treated group [15 (SD 8.4) vs. 11 (1.5) days]. Not surprisingly given the small numbers, no statistically significant effects were seen in any analysis of treatment vs placebo group. The doses of pralidoxime used in the treatment arm of this study (variable between 4 and 12 g/day) did not apparently lead to more rapid reactivation of BuChE.

Pawar 2006

This RCT reported that a number of outcomes were better with a higher dose of pralidoxime for the first 48 hours compared to a lower dose. There was a lower dose requirement for atropine in the first 24 hours (median 6 mg vs 30 mg; difference 24 mg (95% CI 24-26, p<0·0001)), fewer patients needed intubation (64% vs 88%; relative risk=0·72 (95%CI 0·62-0·86, p=0·0001)) and the duration of ventilation was shorter (median 5 days vs 10 days; difference 5 days (95%CI: 5-6, p<0·0001)). Among the secondary outcomes, it is noteworthy that there were also fewer deaths (1% vs 8%; relative risk 0·13 (95%CI: 0·016-0·98; p=0.035)) and fewer episodes of pneumonia (8% vs 35%).

The authors concluded that "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."

Eddleston 2009

This RCT reported that mortality was non significantly higher in patients receiving pralidoxime chloride (2 g loading dose over 20 min, followed by a constant infusion of 0.5 g/h for up to 7 d). 30/121 (24.8%) receiving pralidoxime died, compared with 18/114 (15.8%) receiving placebo (adjusted hazard ratio 1.69 (95% CI 0.88-3.26, p = 0.12)). Pralidoxime did produce substantial and moderate red cell acetylcholinesterase reactivation in patients poisoned by diethyl and dimethyl compounds, respectively. No clinical outcome, adjusted analysis or sub-group analysis showed a favourable effect (all hazard ratios were $\simeq$ or > than 1) for pralidoxime. There were more intubated patients in the pralidoxime group (30/121 (25%) vs 18/114 (16%) crude HR 1.82 (95% CI 1.01-3.28)). While the duration of ventilation was apparently shorter in the pralidoxime treated patients (2.1 days (95% CI 0.8-4.8; n=45) versus 6.5 d (95% CI 1.8-10.1); n=37; p=0.02, Mann Whitney test), some of this reduction was attributed to increased deaths in ventilated patients in the treatment arm.

The authors concluded that "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."

Zhu 2006

This very small RCT (n=24) was unable to show any difference in any outcome between the two arms of the study.

Gu 2008

This RCT reported a very complex three arm trial with each arm having two different flexible dosing strategies (for moderate and severely poisoned patients). The outcomes in all cases favoured the higher dose arms, however it was unclear what the primary outcome(s) and comparison for the analysis were.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Higher dose compared to lower dose for acute organophosphate pesticide poisoning

Patient or population: patients with acute organophosphate pesticide poisoning
Settings:
Intervention: Higher dose
Comparison: lower dose

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	lower dose	Higher dose				
Deaths	**Study population**		**OR 0.38** (0.1 to 1.47)	479 (4 studies)	⊕◯◯◯ **very low**[1,2,3,4]	
	112 per 1000	**46 per 1000** (12 to 156)				
	Medium risk population					
	129 per 1000	**53 per 1000** (15 to 179)				
Intermediate syndrome	**Study population**		**OR 0.94** (0.24 to 3.62)	283 (3 studies)	⊕◯◯◯ **very low**[1,2,3,5,6]	
	244 per 1000	**233 per 1000** (72 to 539)				
	Medium risk population					
	213 per 1000	**203 per 1000** (61 to 495)				
Ventilated	**Study population**		**OR 0.72** (0.08 to 6.35)	272 (2 studies)	⊕◯◯◯ **very low**[1,2,3,6]	

	772 per 1000	**709 per 1000** (213 to 956)
	Medium risk population	
	676 per 1000	**600 per 1000** (143 to 930)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Substantial risk of bias identified in all studies
[2] Worse outcomes with higher dose in Samuel 1995, reverse is true in other studies
[3] Confidence intervals indicate results are consistent with both a substantial risk and benefit from higher doses. Total number of events is much less than 300 for all outcomes. Further imprecision added by variation in doses compared and lack of mechanistic evidence underpinning any of the dosing strategies compared.
[4] There are too few trials to make an informed judgement about the risk of publication bias
[5] Outcome/diagnosis may be subjective
[6] Not all studies provided information about this outcome.

DISCUSSION

Seven RCTs on pralidoxime treatment have been published, involving 845 patients. Three RCTs including 366 patients studied pralidoxime vs placebo and four RCTs including 479 patients compared two or more different doses. The authors of the unfunded studies in particular must be commended for attempting important studies in such a difficult environment. However, most studies did not take into account the type of OP or the timing of the oxime and the published methodology was often unclear. The wide range of doses and durations (Table 1), settings, and types of OP mean that pooling the results (e.g. Analysis 1.1) may not lead to true estimates of effect. It is clear that there may be potential benefit from oximes as AChE activity is clearly increased by treatment (Eddleston 2009; Willems 1993; Thiermann 1997; Worek 1997) and two of the larger RCTs reported benefit from higher doses (Pawar 2006; Gu 2008). However, most RCTs did not report benefit or reported harm. Therefore, we believe a generalised statement cannot be justified from the published results and that the evidence for or against the use of oximes has not yet been established.

There are two key issues which future studies of oximes need to address. Firstly, the patients who might benefit are not clear, particularly at the time of recruitment. A rapid test to measure (or algorithm to predict) if there is substantial AChE inhibition and reactivatable (non-aged) AChE might be useful to only recruit patients that respond into future trials. While this is only a surrogate marker and people can clearly survive despite high degrees of inhibition (Eddleston 2009), it seems unlikely that patients who do not reactivate RBC-AChE will obtain benefit from oximes. There are clearly toxic effects of pralidoxime as noted in the common adverse effects in the RCTs. Indeed the LD50 for pralidoxime chloride in mice (93.6mg/kg - Namba 1971) is only about 3 fold higher than the WHO recommended loading dose (Johnson 2000) and the drug would be expected to further accumulate with the infusion if there was impaired renal function (Kayouka 2009), as is common in severe poisoning.

Secondly, there is the issue of what is the optimal dosing strategy for pralidoxime and should doses be individualised to avoid toxicity. The current WHO-sponsored recommendations for pralidoxime chloride therapy is to give at least 30 mg/kg bolus followed by 8 mg/kg/hr infusion. (The WHO recommendations are based on the doses that are known to be required to rapidly achieve and then maintain a high concentration of pralidoxime. This estimated effective concentration is based on in vitro and animal studies with P2S (Johnson 2000).) Perhaps the clearest answer from our review of the RCTs to date is that this dose does not improve clinical outcomes. Interestingly, although animal studies consistently show benefit from oximes (Thompson 1987) there do not appear to be any animal studies that involve more than short term use of oximes. It may be that the maximum benefit from oximes occurs early on, for adaptive mechanisms mean that even the complete absence of AChE activity is compatible with life (Adler 2004). Further, attempts to completely reactivate inhibited AChE may be unnecessary as activity >30% is usually sufficient for normal NMJ function even in the setting of acute OP poisoning (Thiermann 2005).

Conversely, it is quite likely that both the 'low dose' and the 'high-dose' regimen of pralidoxime used in Vellore did not produce effective plasma concentrations. Pharmacokinetic studies have shown that 1 g given over 30 mins to patients with a mean weight of 72 kg (SD 8.5) falls below a plasma concentration of 4 mg/L within 1.5 hours (Medicis 1996). The weight of the Indian study participants is not given in either paper; however, an estimated mean weight of 45 kg would only increase the effective concentration time by a factor of ~2. In the group receiving the infusion only, it appears doubtful whether an estimated initial dose of 2.8 mg/kg over the first 30 mins would ever give a plasma level that would achieve significant or sustained reactivation. An alternative interpretation of the results of Samuel 1995 would, therefore, be that a loading dose of pralidoxime is required to reach an effective plasma concentration and that a bolus dose alone, while producing an effective concentration for only several hours, offers some benefit.

However, the worse outcome seen in patients who received pralidoxime in Cherian 1997 and Eddleston 2009 suggests that the pralidoxime infusion harms patients. An alternative explanation is that the potential biases in these trials led to exaggerated evidence of harm. Howver, it is clear that in these studies there was no benefit even if the evidence for harm may be an overestimate.

Sicker patients might have been randomised to the intervention arm of Cherian 1997, which had much reduced mean pseudocholinesterase levels at baseline. No information on masking is given and a block size of four was used in both studies. As pointed out by Schulz 1995, such a small non-varying block size can often be unravelled: if treatment assignment becomes known after allocation, a sequence can be easily discerned from the pattern of past assignments giving the risk of selection bias, even if concealment has been adequate. Problems with small fixed block sizes may have compromised allocation concealment in Samuel 1995 and Pawar 2006.

Whether pesticides had dimethyl or diethyl groups was also not controlled for in some studies; this is important as only diethylphosphorylated AChEs are expected to respond to pralidoxime after 12h (Worek 1997; Hansen 1999). Deaths may have occurred in patients ingesting dimethylated compounds who presented after 12 hours when pralidoxime would not be expected to work. A study from Sri Lanka showed that around 70% of OP-poisoned patients had ingested dimethylated compounds (de Silva 1992). This situation may well be similar in other parts of the tropics and since many patients present more than 12 hours after the poisoning, it may be too late for oximes. There are many factors present

in self-poisoning cases in South Asia that would reduce the effectiveness of pralidoxime. The OP dose is often large and the pesticide persistent for several days, resulting in repeated inhibition of any newly reactivated AChE. There is also often a lack of intensive care services and other resources, the absence of which may be far more critical to survival than the use of an antidote (Shivakumar 2006).

AUTHORS' CONCLUSIONS

Implications for practice

Current evidence is insufficient to indicate whether oximes are harmful or beneficial in the management of acute organophosphorus pesticide poisoning. The World Health Organization recommended pralidoxime regimen (30 mg/kg pralidoxime chloride bolus followed by 8 mg/kg/hr infusion) is not supported by outcomes to date. Lower doses have also shown worse outcomes in one RCT. Thus the published RCTs provide limited guidance for clinicians. Despite this there are consistent animal data supporting their effectiveness, when given early. Based on our understanding of the mechanism, *in vitro* and animal data, benefit−risk ratio is more likely to be favourable when they are given early, to patients with serious poisoning by diethyl OPs. However, the RCTs have not defined effective doses or sub-groups that are likely to benefit. Thus use should be confined to clinical trials and situations where better established treatments have proven ineffective.

Implications for research

Further RCTs are required to determine if there are other strategies and regimens that might consistently lead to benefit in some individuals. There are many theoretical and practical reasons why oximes may not be useful and might even be harmful to patients with overwhelming self-poisoning, particularly with late presentations of dimethyl OP. Future studies should attempt to incorporate as many as of the following features as possible:

- to specifically screen for patient sub-groups that may benefit from oximes.
- to explore different doses or incorporate flexible dosing strategies.
- randomisation should be stratified by baseline severity, time to presentation, and class of OP pesticide taken (diethyl or dimethyl).
- the trial should be registered and use predefined sub-group hypotheses.
- RBC-AChE activity and the potential for ex-vivo reactivation should be measured (because of the importance of ageing in determining the usefulness of oxime).

It is noteworthy that a very large number of clinical studies on pralidoxime are being reported from China (Appendix 2) and that flexible dosing strategies seem to be used in nearly all of them. However, much clearer reporting of these studies is required in order to firstly determine whether they are randomised and to assess other aspects of methodological quality. Further the complex regimens need to be described in sufficient detail that they can be replicated or incorporated into protocols. We hope future Chinese trials will take note of the CONSORT guidelines now that these have been translated (Moher 2010).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Cherian 1997

Methods	Randomised double-blind controlled trial.
Participants	110 OP poisoned patients - pralidoxime arm: Male 41/55 (75%); Mean age 28.0 (10.1) years vs. Controls: Male 34/55 (62%); Mean age 26.5 (10.3) years Inclusion: symptomatic OP poisoning (requiring ICU admission). Exclusion: >48hr after poisoning, taken carbamates, renal or hepatic failure, systemic disease, known pregnancy Baseline imbalance in Mean PCE levels: 283.3 (SD 243) IU/L in pralidoxime group vs and 743.7 (SD 1254) IU/L in the control group. In an early abstract including 100 patients there also appeared to be an imbalance in the number of unconscious patients at baseline
Interventions	Pralidoxime chloride (12g by continuous infusion without loading dose over 3 days) vs placebo saline infusion All patients received atropine titrated to maintain pulse rate about 100 bpm, pupils at mid position, normal bowel sounds, clear lungs, with no signs of atropine toxicity
Outcomes	Death [16/55 (Pralidoxime) vs 3/55(control)], intermediate syndrome [36/55 vs 19/55], pneumonia [37/55 vs 22/55] Also reported a regression analysis of mortality reporting odds ratio of 9.2 (95%CI: 1.9-44.7) for pralidoxime treated patients vs controls. [Worse outcomes also reported for females and patients aged >40.]
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Quote: "Patients were randomised using a block randomisation schedule (block size of 4) to receive either a placebo infusion (normal saline) for 3 days or 12 gm of P2AM as an infusion over 3 days."
Allocation concealment?	Unclear risk	Not mentioned in report. Small fixed block size (4) may have allowed subversion of allocation concealment
Blinding? All outcomes	Low risk	Described as double-blind in title and used placebo infusion No details on blinding procedures provided.

Cherian 1997 (*Continued*)

Incomplete outcome data addressed? All outcomes	Low risk	All patients included in analysis.
Free of selective reporting?	Unclear risk	Quote: "Outcome measures analysed were mortality, need for ventilation and duration of ventilation, development of intermediate syndrome and infections." Comment: No primary outcome specified, no power calculation and not registered. However outcomes consistent with previous trial by this group (Samuel 1995).
Free of other bias?	Unclear risk	Power/sample size/premature stopping. No power or sample size calculation presented nor a plan for interim analysis or stopping rules. Analysis of the first 100 randomised patients presented in 1996 abstract with worse outcomes in treatment group. Trial ceased shortly after when 110 patients randomised

Cherian 2005

Methods	Randomised double-blind controlled trial.
Participants	21 OP poisoned patients. Demographics not recorded. Inclusion symptomatic OP poisoning (moderate/severe using Namba scale); Exclusion: no criteria stated Pralidoxime arm: 5/10 (50%) with moderate poisoning; 5/10 (50%) with severe poisoning Controls: 6/11 (55%) with moderate poisoning; 5/11 (45%) with severe poisoning
Interventions	Pralidoxime chloride (4g/day for moderate poisoning or 12g/day for severe poisoning by continuous infusion without loading dose over 3 days) vs placebo saline infusion Atropine given to all patients but dosing strategy not recorded. 7/10 & 4/11 patients ventilated
Outcomes	Deaths (1/10 vs 1/11) and complications ("mainly nosomoial infections") (4/10 vs 6/11) recorded However, much of the analysis of the trial was comparing BuChe levels with OP poisoning complications and outcomes rather than to examining effects of pralidoxime treatment
Notes	The decision as to when the two different doses of pralidoxime was used in the treatment arm is not transparent. There are also insufficient details on demographics/poisoning characteristics

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Cherian 2005 (*Continued*)

Adequate sequence generation?	Unclear risk	Quote: "Only moderate and severe cases, as assessed by the Namba scale were included. These two groups of patients were randomised to receive PAM or placebo." Comment: Randomisation sequence, method not recorded and unclear if stratified by clinical severity. The Namba scale has not been validated as a useful method of assessing severity and the BuChe component has been demonstrated to be flawed (Eddleston 2008a).
Allocation concealment?	Unclear risk	Not recorded.
Blinding? All outcomes	Low risk	Quote: "Both patients and the investigator were blinded." Title also states double-blind, and used placebo infusion, however no details on blinding procedure or how dose was adjusted if blinded
Incomplete outcome data addressed? All outcomes	Low risk	All patients included in analysis.
Free of selective reporting?	Unclear risk	Not registered.
Free of other bias?	Unclear risk	Sample size: Quote: "Sample size and statistical analysis. As this is mainly a biochemical/physiological study, 10 cases of severe poisoning and 11 cases of moderate poisoning were studied using the maximum recommended doses of PAM." Comment: This does not indicate whether the number to be enrolled was decided in advance or a post-hoc decision was made to terminate the study

Eddleston 2009

Methods	Randomised double-blind placebo controlled trial.
Participants	235 OP poisoned patients in two centres. Pralidoxime arm: Males 96/121 (79%); Median age 31 (22-48) years. Placebo arm: Males 92/114 (81%); Median age 29.5 (23-42) years About 48% were poisoned by diethyl-OP and 31% by dimethyl-OP (the rest were unknown/mixed or other). Diethyl OP included chlorpyrifos, quinalphos, and diazinon; dimethyl OP included dimethoate, fenthion, phenthoate, and oxydemeton-methyl (all are WHO Class II toxicity pesticides)

Eddleston 2009 (*Continued*)

	Inclusion: symptomatic OP poisoning (requiring atropine). Exclusion: <14 years of age, known pregnancy, receipt of pralidoxime at transferring hospital; previous recruitment in this RCT
Interventions	2 gm pralidoxime chloride loading dose, 0.5 gm/hr infusion for a maximum of 7 days vs placebo loading dose and infusion
Outcomes	Primary Outcome: • All-cause mortality at hospital discharge Secondary Outcomes: • Percentage of patients requiring intubation • Time requiring ventilation • Percentage of patients developing the intermediate syndrome (cranial nerve palsies and/or proximal weakness, without distal weakness, after resolution of the cholinergic crisis) Detailed adverse events reported. Also report subgroup analyses & analysis of outcomes adjusted for randomisation imbalances, reactivation and poisoning characteristics
Notes	Outcomes above from ISRCT registration - intermediate syndrome not reported in published paper

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Quote: "The random allocation sequence was generated by computer and incorporated into a programme written for recruitment, randomisation, and event recording. Stratified block randomisation was performed using: (i) chemical structure (diethyl, dimethyl, unknown/other); (ii) reported time between poisoning and recruitment (4 h; 4-12 h; 12 h; unknown); (iii) status on admission (GCS 14-15/15, GCS 14), and (iv) allocation in a concurrent RCT of activated charcoal [25]. The allocation sequences were generated independently by the statistician and implemented by the programmer, neither of whom interacted with patients. Variable block sizes were used to allocate patients in equal numbers to each treatment group using Stata v. 7 software (ralloc subroutine version 3. 2.5). Block randomisation schedule (variable block size), stratified by type of poison (dimethyl/diethyl); time since poison

		ingestion, severity of poisoning (GCS), allocation to concurrent RCT of activated charcoal
Allocation concealment?	Low risk	Quote: "Participants were recruited and randomised by a study doctor at the bedside using a dedicated handheld computer at each study hospital. Randomisation occurred after baseline data had been entered, and could not be altered by study doctors. The recruiting doctor could not predict allocation accurately before randomisation."
Blinding? All outcomes	Low risk	Quote: "The study was double-blind. The pralidoxime and placebo were provided in batches of vials, identical except for a serial number starting with one of two letters: A or B, C or D, etc. At randomisation, the computer program specified a letter; vials with that letter were used for that patient. At intervals, the letter pairs were shifted to the next pair to reduce the risk of unblinding."
Incomplete outcome data addressed? All outcomes	Low risk	Trial flow diagram indicates outcomes reported on all randomised patients
Free of selective reporting?	Low risk	Registered trial - all pre-specified outcomes and adverse outcomes reported except for the secondary outcome of "intermediate syndrome" which proved to have multiple definitions in practice
Free of other bias?	Unclear risk	Premature stopping: Quote: "An independent data monitoring committee (IDMC) was established for this and the concurrent trial [25]. Interim analyses were to be supplied by the trial statistician to the IDMC Chair as often as requested. In the light of interim data, and emerging evidence from other studies, the IDMC then informed the principal investigator if in their view there was proof beyond reasonable doubt that the data indicated that any part of the protocol under investigation became clearly indicated or contraindicated, or it was evident that no clear outcome would be obtained. The trial stopped after the first interim analysis due

Eddleston 2009 (*Continued*)

		to lack of recruitment." "Unfortunately, discussion of the results of an RCT [29] performed in Baramati, India, that suggested marked benefit from pralidoxime at a seminar in August 2005, resulted in loss of equipoise (the perception of treatments being of equal value) by clinicians, a fall off in recruitment, and early termination of the trial."

Gu 2008

Methods	'Randomised' by use of 'Arabic numbers'. No mention of ratio, blinding or allocation concealment Unequal numbers in 3 groups 56, 56 & 75. (?? randomised in 3:3:4 ratio.)
Participants	187 People with moderate or severe acute organophosphorus poisoning. Age range 15-79, mean age 41.6 (SD 20.4) OPs ingested: methamidophos 43, dimethoate 34, folimat 31, dichlorvos 22, parathion 19, isocarbophos 16, metrifonate 10, mixed 7, unknown OP 5 Setting: Emergency Medicine Service, Zhejiang, China.
Interventions	complex comparison of 3 regimens of pralidoxime chloride with different treatment given post randomisation for moderate and severe poisonings: A: 1g or 2g loading IV, then infusion 250-400 mg/hr for 2-4 days vs. B: Moderate poisoning: 1g im first, repeated 1g q1hr for 3 doses, 1g q4hr to 24hrs.1g q6hr for 1-2days. Stop treatment if AChE activity increases to 50% of normal Severe poisoning: 2g oxime im/iv first, then 1g q1hr for 3 doses, then 1g q2hr for 3 doses, 1g q4hr for 2-4 days. Stop treatment if AChE activity increases to 50% normal value vs. C: Moderate poisoning: 1g twice a day; Severe poisoning: 2g 2-3 times a day.
Outcomes	Death, intermediate syndrome, complications incl. pneumonia, hospital stay, atropine dose Deaths - A:1/56 vs. B: 2/56 vs. C:9/75. intermediate syndrome - A:6/56 vs. B:5/56 vs. C:16/75 complications including pneumonia - A:5.7% vs. B:72.5% vs. C:66.2% mean hospital stay - A:8.81 days (SD 4.94) vs. B:9.45 (3.21) vs. C:12.56 (6.35) mean total atropine dose - A:44.05 mg (SD12.59) vs. B:44.56 (8.26) vs. C:86.20 (6.28)
Notes	Comparison of A+B vs C used for high vs. low dose comparison in pooled analysis as cumulative dose in A & B probably fairly similar. (for example, in first 24 hours group A would receive 7 to 11.6g, group B would receive 8 to 11g, and group C would receive

Gu 2008 (*Continued*)

	2 to 6 g)

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	'Arabic numbers' - presumably from a table of random numbers - but quite substantial imbalance in numbers in each group: 56, 56 & 75. (?? randomised in 3:3:4 ratio.)
Allocation concealment?	Unclear risk	Not described.
Blinding? All outcomes	High risk	Not described or likely given complex regimen.
Incomplete outcome data addressed? All outcomes	Unclear risk	Not mentioned.
Free of selective reporting?	Unclear risk	Not described.
Free of other bias?	Unclear risk	Much higher atropine dose in group C may have resulted from lack of blinding and also have lead to adverse outcomes (although interpreted as being an outcome of less effective treatment)

Pawar 2006

Methods	Single-centre, open randomised controlled trial.
Participants	200 OP poisoned patients. Males 57/100 (57%); Median age 28 (22-33) years vs. Males 52/100 (52%); Median age 29 (22-35) years Inclusion symptomatic OP poisoning; Exclusion <12 years of age, systemic disease, known pregnancy, >24hr after poisoning, and failure to resuscitate in emergency room ("These severely ill patients were excluded from our trial and were not admitted to the hospital, but transferred to the nearby government hospital. Our study population was therefore confined to moderately severe cases of poisoning.") There was a very high degree of standard other treatment provided compared to the other developing country studies: "This (ICU) unit has a ratio of one nurse, one doctor, and one ventilator to every two patients." 66% of patients were intubated at baseline
Interventions	2 gm pralidoxime iodide loading dose, 1.0 gm/hr infusion for 48 hrs then 1.0 gm/4hr infusion until weaned of ventilation ("High dose") vs. 2 gm loading dose, 1.0 gm/4hr infusion for 48 hrs then 1.0 gm/4hr infusion until weaned of ventilation ("Low dose")
Outcomes	Primary: • Median atropine dose required in first 24 hours

Pawar 2006 (*Continued*)

	• number of days ventilated and required ICU care • proportion of patients who required intubation or developed intermediate syndrome Secondary: • Deaths, • Mean systolic and diastolic blood pressure (BP) in first 24 hours • pneumonia (aspiration or ventilator-associated) Also reported subgroup analyses based on type of OP ingested Median days ventilated: 5 (4 to 5) vs. 10 (8 to 12), p<0·0001 Median atropine dose in first 24 h (mg): 6 (4 to 6) vs. 30 (25 to 45), p <0·0001 Neck muscle weakness: 80% vs. 94%, p=0·0054 Intubated during admission: 64% vs. 88%, p=0·0001 Intubated after randomisation: 1/37 vs. 19/31, p <0·0001 (Intubated before randomisation: 63/100 vs 69/100) Deaths: 1% vs. 8%, p= 0·0349 Pneumonia: 8% vs. 35%, p <0·0001 Mean systolic blood pressure in first 24h (mm Hg): 136·2 (4·97) vs. 115·4 (SD 6·1), p<0·0001 Mean diastolic blood pressure in first 24h (mm Hg) 84·1 (2·56) vs. 75·6 (SD 4·96), p<0·0001 (higher vs. lower dose)
Notes	Outcomes above listed on clinicaltrials.gov web site - however, intermediate syndrome and length of ICU stay were not reported in paper

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Quote: "Enrolled patients were then randomly assigned by use of a block randomisation schedule, which was independently generated by a programmer who had no role in recruitment, treatment, or assessment of patients. The schedule remained concealed until after the trial's completion. Allocation sequences were prepared in sets, each of which contained ten blocks with four numbered chits in each block. For each set of 40 patients, one of the ten blocks was chosen at random without replacement, and was then used for the next four consecutive patients to enrol. From this numbered block, one of the four numbered chits was chosen. On the basis of these two numbers, the computer program then allocated each patient to either the control or study group."

Pawar 2006 (*Continued*)

Allocation concealment?	Unclear risk	Quote: "one of the ten blocks was chosen at random without replacement, and was then used for the next four consecutive patients to enrol. From this numbered block, one of the four numbered chits was chosen. On the basis of these two numbers, the computer program then allocated each patient to either the control or study group." Quote: "Participants were unaware of their allocation to control or study groups. Duty doctors were unaware of the allocation sequence but were aware of the allocation once each patient was allocated to the study or control group." Comment: It is unclear if with a fixed block of 4 and an unblinded trial whether individual doctors may have been able to guess the next treatment to be assigned
Blinding? All outcomes	High risk	Quotes: "Open randomised controlled trial"; "Participants were unaware of their allocation to control or study groups. Duty doctors were unaware of the allocation sequence but were aware of the allocation once each patient was allocated to the study or control group." "Aspiration or ventilator-associated pneumonia was diagnosed by a consultant physician who was unaware of the patient's allocation, on the basis of the patient's history, clinical picture, and chest radiographs."
Incomplete outcome data addressed? All outcomes	Low risk	Flow chart indicates all randomised patients included in analysis
Free of selective reporting?	Unclear risk	Five primary outcomes listed on trial registration and two of these (probably the least objective two) were not reported

Samuel 1995

Methods	Randomised double-blind controlled trial.
Participants	72 OP poisoned patients. Males 26/36 (72%); Mean age 25.2 (10.8) years vs. Males 26/36 (72%); Mean age 24.9 (7.5) years Inclusion symptomatic OP poisoning (requiring ICU admission); Exclusion >48hr after poisoning, taken carbamates, renal or hepatic failure, systemic disease, known pregnancy

	OP ingested: methylparathion (11), phosphamidon (12), monocrotophos (15), quinalphos (17), malathion (4), unknown (16). (from Table 2 in Samuel 1995 and Table 1 in 1996 report - note numbers of each OP ingested in Table 6 of Samuel 1995 are slightly different to those listed above, but in any case the majority of poisonings are with dimethyl OP)
Interventions	Pralidoxime infusion (12g given as a reducing infusion over four days) vs bolus dose (1g STAT IV)
Outcomes	Death, intermediate syndrome, pneumonia. Also report subgroup analyses based on time to treatment and type of poison ingested. Deaths: 8/36 vs 5/36 Intermediate syndrome: 20/36 vs 13/36 Duration of lCU stay (mean days): 6.8(5.0) vs. 5.9(4.0) Ventilated: 24/36 vs. 17/36 Mean duration of ventilation (hours): 180.9 (SD 124.7) vs. 164.1 (114.9) Infections: 15/36 vs. 10/36 Mean atropine dose (mg/day): 44.2 (40.0) vs. 42.7 (41.6) (12 g infusion vs. 1g bolus)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Quote: "Patients were randomised using a block randomisation schedule (block size of 4)"
Allocation concealment?	Unclear risk	Not discussed Small fixed block size (4) may have allowed subversion of allocation concealment
Blinding? All outcomes	Low risk	Quote: "72 patients .... were randomised (26 males and 10 females in each group) to receive either PAM 1 gram as an intravenous bolus dose immediately after admission followed by sham IV infusion of 0.9% saline for the next four days or a sham IV bolus injection of 0.9% saline followed by PAM twelve grams as a continuous infusion over a period of four days. The sham bolus dose and the infusion of PAM were started immediately after admission." "All other supportive measures were given as required, and the day to day decisions on management were made by the concerned unit Physician. Both patients and the in-

Samuel 1995 (*Continued*)

		vestigator were blinded to the study." Comment: No details were provided on who was unblinded and prepared treatment and sham infusions
Incomplete outcome data addressed? All outcomes	Low risk	No flow chart. Outcomes appear to be reported on all 72 randomised patients
Free of selective reporting?	Low risk	Trial was not registered but all relevant outcomes reported. Quote: "The subgroup analysis of the data suggests that the time of administration of P2AM may be an important factor which determines outcome. A significantly lower incidence of intermediate syndrome was noted in the group which received 1 gm of P2AM within 12 hours of ingestion of the OP compound Comment: Two post-hoc analyses clearly identified as such.
Free of other bias?	Unclear risk	Power/Sample size/Stopping rules: Quote: "One regimen was considered to be superior over the other if (1) length of stay decreased by 1 day or (2) the duration of ventilation was reduced by 24 hours. Based on these, sample size calculations revealed that 25 patients needed to be recruited in each arm." Comment: in hindsight, the trial appears underpowered even for these outcomes

Zhu 2006

Methods	"Randomised" but no method mentioned.
Participants	24 patients with severe acute organophosphorus poisoning (mostly methamidophos, but also dimethoate (2), 3911 (1), dichlorvos (1)). 7 males & 17 females. Age range 16-76, mean age 33.5 (SD:18.6) Setting: Emergency Medicine Service, Neimenggu, China.
Interventions	Higher dose: pralidoxime chloride 2g IM then 1g IM/hr for 2hrs then 1gm IM every 2 hours for 24 hours; then 1g IM q8h for 48hrs, but treatment could be stopped depending on AChE Lower dose: pralidoxime 1g IM q3hrs for 24hrs, 1g q8hrs for another 24 hrs, stopped depending on AChE

Zhu 2006 (*Continued*)

Outcomes	Death, intermediate syndrome, time to atropinisation being achieved Deaths: 1/12 vs 3/12. Intermediate syndrome:1/12 vs 1/12. Atropinisation time: 2.34±0.36 vs 2.5±0.43 hr. (High vs low dose respectively.)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Randomisation method not described.
Allocation concealment?	Unclear risk	Not mentioned.
Blinding? All outcomes	Unclear risk	Not mentioned.
Incomplete outcome data addressed? All outcomes	Unclear risk	Not mentioned.
Free of selective reporting?	Unclear risk	Not registered.
Free of other bias?	Unclear risk	No description of success with follow up or participant study flow

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abdollahi 1995	Not an RCT (non-randomised comparative study).
Balali-Mood 1998	Not an RCT (non-randomised comparative study).
Cheng 2005	Not an RCT (historical study).
Chugh 2005	Not an RCT (non-randomised comparative study).
Dadan 1998	Not an RCT (observational study).
de Silva 1992	Not an RCT (non-randomised comparative study).
Duan 2006	No mortality information or data on secondary outcomes.

(*Continued*)

Duval 1991	Not an RCT (non-randomised comparative study).
Eyer 2007	Not an RCT (review with case studies).
Eyer 2009	Not an RCT (observational study).
Guo 2008	No mortality information or data on secondary outcomes.
Hu 2008	No mortality information or data on secondary outcomes.
Kou 2008	Not an RCT.
Li 2003	Not an RCT (non-randomised comparative study).
Li 2009	Not an RCT (non-randomised comparative study).
Shivakumar 2006	Not an RCT (non-randomised comparative study).
Sidell 1973	Not an RCT (observational study).
Sidell 1974	Not an RCT (case reports).
Sungur 2001	Not an RCT (observational study).
Tang 2005	Not an RCT (non-randomised comparative study).
Xue 1985	Not an RCT (review of observational studies).
Yang 2009	No mortality information or data on secondary outcomes.
Yuan 2003	Not an RCT (observational study).
Yue 2007	Not an RCT.
Zhang 2003	No mortality information or data on secondary outcomes.
Zhang 2005	Not an RCT (non-randomised comparative study).
Zheng 2000	Not an RCT (non-randomised comparative study).

DATA AND ANALYSES

Comparison 1. Oxime vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Deaths	3	366	Odds Ratio (M-H, Random, 95% CI)	2.68 [0.93, 7.72]
2 Intermediate syndrome	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
3 Ventilated	3	366	Odds Ratio (M-H, Random, 95% CI)	2.00 [0.81, 4.95]

Comparison 2. Higher dose vs lower dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Deaths	4	479	Odds Ratio (M-H, Random, 95% CI)	0.38 [0.10, 1.47]
2 Intermediate syndrome	3	283	Odds Ratio (M-H, Random, 95% CI)	0.94 [0.24, 3.62]
3 Ventilated	2	272	Odds Ratio (M-H, Random, 95% CI)	0.72 [0.08, 6.35]

Analysis 1.1. Comparison 1 Oxime vs placebo, Outcome 1 Deaths.

Review: Oximes for acute organophosphate pesticide poisoning

Comparison: 1 Oxime vs placebo

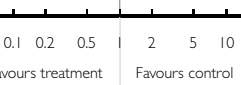
Outcome: 1 Deaths

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Cherian 1997	16/55	3/55		33.9 %	7.11 [1.94, 26.12]
Cherian 2005	1/10	1/11		11.1 %	1.11 [0.06, 20.49]
Eddleston 2009	30/121	18/114		55.1 %	1.76 [0.92, 3.37]
Total (95% CI)	**186**	**180**		**100.0 %**	**2.68 [0.93, 7.72]**

Total events: 47 (Treatment), 22 (Control)

Heterogeneity: $Tau^2 = 0.42$; $Chi^2 = 3.82$, df = 2 (P = 0.15); $I^2 = 48\%$

Test for overall effect: Z = 1.83 (P = 0.067)

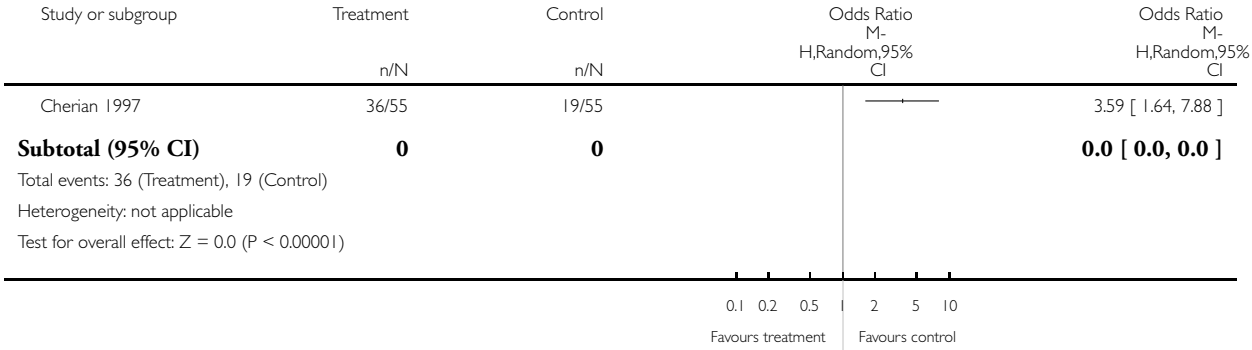


Analysis 1.2. Comparison 1 Oxime vs placebo, Outcome 2 Intermediate syndrome.

Review: Oximes for acute organophosphate pesticide poisoning

Comparison: 1 Oxime vs placebo

Outcome: 2 Intermediate syndrome

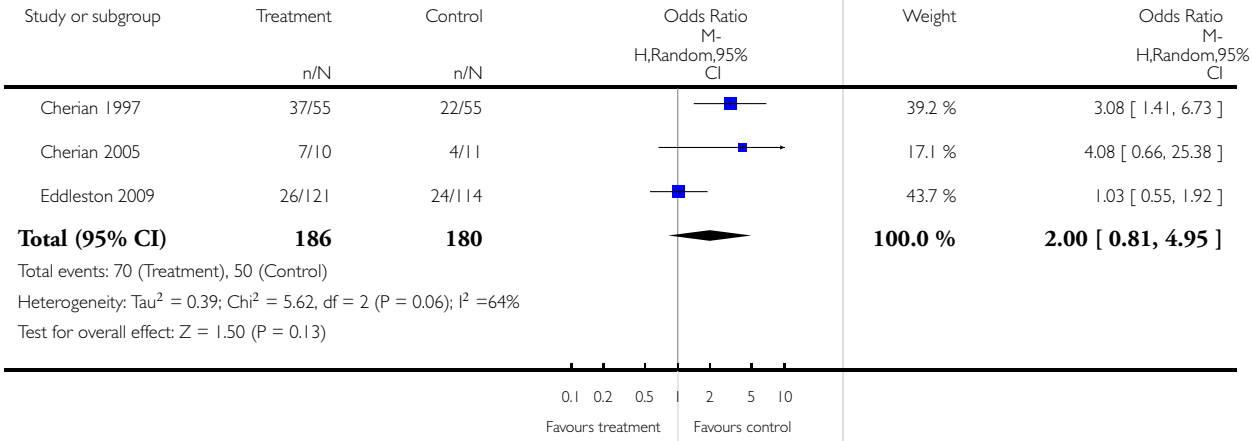


Analysis 1.3. Comparison 1 Oxime vs placebo, Outcome 3 Ventilated.

Review: Oximes for acute organophosphate pesticide poisoning

Comparison: 1 Oxime vs placebo

Outcome: 3 Ventilated



Analysis 2.1. Comparison 2 Higher dose vs lower dose, Outcome 1 Deaths.

Review: Oximes for acute organophosphate pesticide poisoning

Comparison: 2 Higher dose vs lower dose

Outcome: 1 Deaths

Study or subgroup	Higher dose n/N	Lower dose n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Gu 2008	3/108	9/75		29.8 %	0.21 [0.05, 0.80]
Pawar 2006	1/100	8/100		21.0 %	0.12 [0.01, 0.95]
Samuel 1995	8/36	5/36		31.3 %	1.77 [0.52, 6.05]
Zhu 2006	1/12	3/12		17.9 %	0.27 [0.02, 3.09]
Total (95% CI)	**256**	**223**		**100.0 %**	**0.38 [0.10, 1.47]**

Total events: 13 (Higher dose), 25 (Lower dose)

Heterogeneity: $Tau^2 = 1.14$; $Chi^2 = 7.83$, df = 3 (P = 0.05); $I^2 = 62\%$

Test for overall effect: Z = 1.40 (P = 0.16)

Test for subgroup differences: Not applicable

Analysis 2.2. Comparison 2 Higher dose vs lower dose, Outcome 2 Intermediate syndrome.

Review: Oximes for acute organophosphate pesticide poisoning

Comparison: 2 Higher dose vs lower dose

Outcome: 2 Intermediate syndrome

Study or subgroup	Higher dose n/N	Lower dose n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Gu 2008	11/112	16/75		43.3 %	0.40 [0.17, 0.92]
Samuel 1995	20/36	13/36		41.3 %	2.21 [0.86, 5.69]
Zhu 2006	1/12	1/12		15.4 %	1.00 [0.06, 18.08]
Total (95% CI)	**160**	**123**		**100.0 %**	**0.94 [0.24, 3.62]**

Total events: 32 (Higher dose), 30 (Lower dose)

Heterogeneity: $Tau^2 = 0.92$; $Chi^2 = 7.06$, df = 2 (P = 0.03); $I^2 = 72\%$

Test for overall effect: Z = 0.10 (P = 0.92)

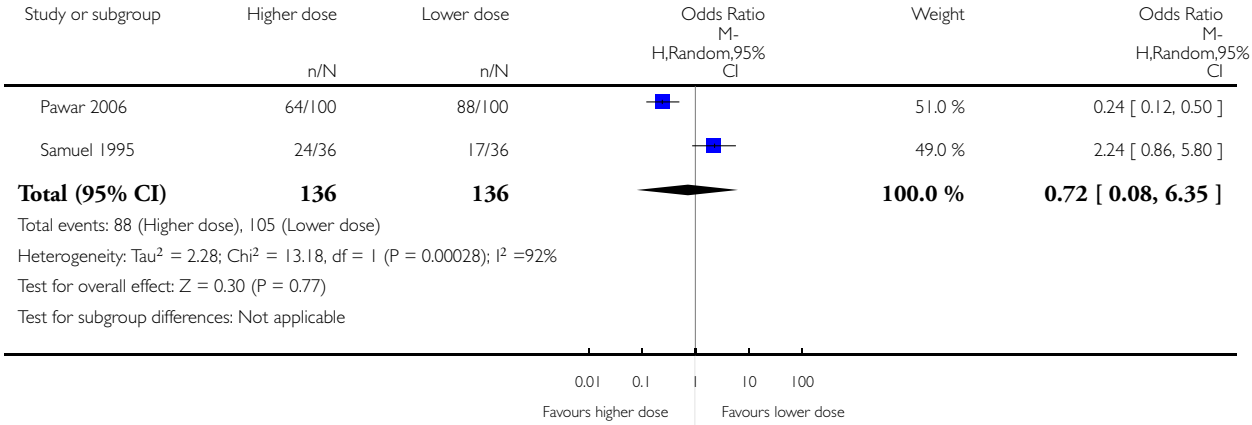
Test for subgroup differences: Not applicable

Analysis 2.3. Comparison 2 Higher dose vs lower dose, Outcome 3 Ventilated.

Review: Oximes for acute organophosphate pesticide poisoning

Comparison: 2 Higher dose vs lower dose

Outcome: 3 Ventilated



ADDITIONAL TABLES

Table 1. Doses of pralidoxime cation administered in each arm of the RCTs

Trial	Salt	pralidoxime cation per g of salt	Arm 1 cation dose	Arm 2 cation dose
Samuel 1995	Chloride§	0.795 g	0.8 g loading dose over 1-5 min	No loading dose, then infusion of 4.8 g over 1st 24 h, 2.4 g over 2nd 24 h, 1.6 g over 3rd 24 h, and 0.8 g over 4th 24 h
Cherian 1997	Chloride§	0.795 g	None	No loading dose, then infusion of 9.5 g over 3 d #
Cherian 2005	Chloride	0.795 g	None	No loading dose, then infusion of 9.5 g or 28.6 g over 3 d
Pawar 2006	Iodide	0.52 g	1.04 g loading dose over 30 min, then 0.52 infused over 1 hr every	1.04 g loading dose over 30 min, then 0.52 g/h constant infusion for 48 h, then 0.52 g

Table 1. Doses of pralidoxime cation administered in each arm of the RCTs (*Continued*)

			4 h	infused over 1 h every 4 h
Eddleston 2009	Chloride	0.795 g	None	1.6 g loading dose over 20 min, then 0.4 g/h constant infusion for up to 7 d
Zhu 2006	Chloride	0.795 g	0.8g IM q3hrs for 24hrs, 0. 8 g q8hrs for another 24 hrs, stopped depending on AChE	1.6 g IM then 0.8 g IM/hr for 2hrs then 0.8 gm IM q2h for 24h then 1g IM q8h for 48hrs, stopped depending on AChE
Gu 2008	Chloride	0.795 g	Flexible, up to 4.8g on first day	Flexible, up to 9.3g on first day.

§ Not stated in papers. Personal communication, Dr. J. V. Peter.
# Exact dosage regimen over the 3 d not stated in paper.

APPENDICES

Appendix 1. Electronic searches

Cochrane Injuries Group Specialised Register (searched 10 Sept 2009-all years)
1.oxime* or hydroxyimin* or ketoxime* or Acetaldoxime* or Aldoxime* or Alloxime* or Amidox or Benolizime* or Diiodide* or diclofurime or dimethylglyoxime or "Diacetyl Oxime*" or Enviroxime* or "Heterocyclic Oxime*" or Hydroxyimine* or "Hexamethylenedicarbamic Acid*" or "Hydroxyiminomethylpyridinium Dichloride" or uvoxamine or methylenebis or Obidoxime* or Pralidoxime* or Pyrimidoxime* or Salicylaldoxime* or Teboroxime* or technetium or trimedoxime or upenazime* or uvoxamine or viroxime* or Zinviroxime*
2.organopyrophosphate* or organophos* or organothiophos* or OP or insecticide* or pesticide* or acephate or "azinphos ethyl" or "azinphos methyl" or chlorpyrifos or coumafos or crufomate or cyanofenphos or cythioate or dichlorvos or dicrotophos or dimethoate or dimpylate or disulfoton or ethion or ethoprop or etrimfos or fenitrothion or fensulfothion or fenthion or fonofos or formothion or Isofenphos or leptophos or malaoxon or malathion or methamidophos or methidathion or metrifonate or mevinphos or mipafox or stirofos or temefos or terbufos or triazophos or "tributyl phosphorotrithioite"
3.1 and 2

MEDLINE (Ovid SP) 1950 to September Week 1 2009
1.exp Oximes/
2.(oxime* or hydroxyimin* or ketoxime* or Acetaldoxime* or Aldoxime* or Alloxime* or Amidox or Benolizime* or Diiodide* or diclofurime or dimethylglyoxime or Diacetyl Oxime* or Enviroxime* or Heterocyclic Oxime* or Hydroxyimine* or Hexamethylenedicarbamic Acid* or Hydroxyiminomethylpyridinium Dichloride or uvoxamine or methylenebis or Obidoxime* or Pralidoxime* or Pyrimidoxime* or Salicylaldoxime* or Teboroxime* or technetium or trimedoxime or upenazime* or uvoxamine or viroxime* or Zinviroxime*).mp.
3.1 or 2
4.exp Phosphoric Acid Esters/po, ae [Poisoning, Adverse Effects]
5.exp Organophosphorus Compounds/po, ae [Poisoning, Adverse Effects]
6.exp Insecticides/po, ae [Poisoning, Adverse Effects]
7.(organopyrophosphate* or organophos* or organothiophos* or OP).mp.

8.((methyl* adj1 phosph*) or (organi* adj1 phosphate*)).mp.
9.(phosph* adj2 (acid* or diester* or ester* or organic*)).mp.
10.(insecticide* or acephate or azinphos ethyl or azinphos methyl or chlorpyrifos or coumafos or crufomate or cyanofenphos or cythioate or dichlorvos or dicrotophos or dimethoate or dimpylate or disulfoton or ethion or ethoprop or etrimfos or fenitrothion or fensulfothion or fenthion or fonofos or formothion or Isofenphos or leptophos or malaoxon or malathion or methamidophos or methidathion or metrifonate or mevinphos or mipafox or stirofos or temefos or terbufos or triazophos or tributyl phosphorotrithioite).mp.
11.(pesticide* or armin or clofenvinfos or edifenphos or fenamiphos or fenclofos or phenthoate or thiometon or Vamidothion).mp.
12.or/4-11
13.3 and 12
14.randomi?ed.ab,ti.
15.randomized controlled trial.pt.
16.controlled clinical trial.pt.
17.placebo.ab.
18.clinical trials as topic.sh.
19.randomly.ab.
20.trial.ti.
21.14 or 15 or 16 or 17 or 18 or 19 or 20
22.(animals not (humans and animals)).sh.
23.21 not 22
24.13 and 23
25.(2003* or 2004* or 2005* or 2006* or 2007* or 2008* or 2009*).em.
26.25 and 24

CENTRAL (The Cochrane Library 2009, Issue 3) (all years)

#1MeSH descriptor Organophosphorus Compounds explode all trees with qualifiers: AE,PO
#2MeSH descriptor Phosphoric Acid Esters explode all trees with qualifiers: AE,PO
#3MeSH descriptor Insecticides explode all trees with qualifiers: AE,PO
#4organopyrophosphate* or organophos* or organothiophos* or OP
#5(methyl* next phosph*) or (organi* next phosphate*)
#6(phosph*) near2 (acid* or diester* or ester* or organic*)
#7(insecticide* or acephate or azinphos ethyl or azinphos methyl or chlorpyrifos or coumafos or crufomate or cyanofenphos or cythioate or dichlorvos or dicrotophos or dimethoate or dimpylate or disulfoton or ethion or ethoprop or etrimfos or fenitrothion or fensulfothion or fenthion or fonofos or formothion or Isofenphos or leptophos or malaoxon or malathion or methamidophos or methidathion or metrifonate or mevinphos or mipafox or stirofos or temefos or terbufos or triazophos or tributyl phosphorotrithioite)
#8pesticide* or armin or clofenvinfos or edifenphos or fenamiphos or fenclofos or phenthoate or thiometon or Vamidothion
#9(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)
#10 MeSH descriptor Oximes explode all trees
#11 oxime* or hydroxyimin* or ketoxime* or Acetaldoxime* or Aldoxime* or Alloxime* or Amidox or Benolizime* or Diiodide* or diclofurime or dimethylglyoxime or Diacetyl Oxime* or Enviroxime* or Heterocyclic Oxime* or Hydroxyimine* or Hexamethylenedicarbamic Acid* or Hydroxyiminomethylpyridinium Dichloride or uvoxamine or methylenebis or Obidoxime* or Pralidoxime* or Pyrimidoxime* or Salicylaldoxime* or Teboroxime* or technetium or trimedoxime or upenazime* or uvoxamine or viroxime* or Zinviroxime*
#12 (#10 OR #11)
#13 (#9 AND #12)

EMBASE (Ovid SP) 1980 to August 2009 (Week 36)

1.exp Oxime/
2.(oxime* or hydroxyimin* or ketoxime* or Acetaldoxime* or Aldoxime* or Alloxime* or Amidox or Benolizime* or Diiodide* or diclofurime or dimethylglyoxime or Diacetyl Oxime* or Enviroxime* or Heterocyclic Oxime* or Hydroxyimine* or Hexamethylenedicarbamic Acid* or Hydroxyiminomethylpyridinium Dichloride or uvoxamine or methylenebis or Obidoxime* or Pralidoxime* or Pyrimidoxime* or Salicylaldoxime* or Teboroxime* or technetium or trimedoxime or upenazime* or uvoxamine or viroxime* or Zinviroxime*).mp.
3.1 or 2
4.exp organophosphate/
5.exp organophosphate pesticide/

6.exp Insecticide/
7.(organopyrophosphate* or organophos* or organothiophos* or OP).mp.
8.((methyl* adj1 phosph*) or (organi* adj1 phosphate*)).mp.
9.(phosph* adj2 (acid* or diester* or ester* or organic*)).mp.
10.(insecticide* or acephate or azinphos ethyl or azinphos methyl or chlorpyrifos or coumafos or crufomate or cyanofenphos or cythioate or dichlorvos or dicrotophos or dimethoate or dimpylate or disulfoton or ethion or ethoprop or etrimfos or fenitrothion or fensulfothion or fenthion or fonofos or formothion or Isofenphos or leptophos or malaoxon or malathion or methamidophos or methidathion or metrifonate or mevinphos or mipafox or stirofos or temefos or terbufos or triazophos or tributyl phosphorotrithioite).mp.
11.(pesticide* or armin or clofenvinfos or edifenphos or fenamiphos or fenclofos or phenthoate or thiometon or Vamidothion).mp.
12.or/4-11
13.3 and 12
14.(2003* or 2004* or 2005* or 2006* or 2007* or 2008* or 2009*).em.
15.13 and 14
16.exp Randomized Controlled Trial/
17.exp controlled clinical trial/
18.randomi?ed.ab,ti.
19.placebo.ab.
20.*Clinical Trial/
21.randomly.ab.
22.trial.ti.
23.16 or 17 or 18 or 19 or 20 or 21 or 22
24.exp animal/ not (exp human/ and exp animal/)
25.23 not 24
26.25 and 15

ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) 1970 to Sept 2009 and ISI Web of Science: Conference Proceedings Citation Index- Science (CPCI-S) 1990 to Sept 2009

1.TS=(oxime* or hydroxyimin* or ketoxime* or Acetaldoxime* or Aldoxime* or Alloxime* or Amidox or Benolizime* or Diiodide* or diclofurime or dimethylglyoxime or Diacetyl Oxime* or Enviroxime* or Heterocyclic Oxime* or Hydroxyimine* or Hexamethylenedicarbamic Acid* or Hydroxyiminomethylpyridinium Dichloride or uvoxamine or methylenebis or Obidoxime* or Pralidoxime* or Pyrimidoxime* or Salicylaldoxime* or Teboroxime* or technetium or trimedoxime or upenazime* or uvoxamine or viroxime* or Zinviroxime*)
2.TS=(organopyrophosphate* or organophos* or organothiophos* or OP) OR TS=((methyl* SAME phosph*) or (organi* SAME phosphate*)) OR TS=(insecticide* or pesticide* or acephate or azinphos ethyl or azinphos methyl or chlorpyrifos or coumafos or crufomate or cyanofenphos or cythioate or dichlorvos or dicrotophos or dimethoate or dimpylate or disulfoton or ethion or ethoprop or etrimfos or fenitrothion or fensulfothion or fenthion or fonofos or formothion or Isofenphos or leptophos or malaoxon or malathion or methamidophos or methidathion or metrifonate or mevinphos or mipafox or stirofos or temefos or terbufos or triazophos or tributyl phosphorotrithioite)
3.1 and 2
4.Topic=((singl* OR doubl* OR trebl* OR tripl*) SAME (blind* OR mask*))
5.Topic=(randomised OR randomized OR randomly OR random order OR random sequence OR random allocation OR randomly allocated OR at random OR randomized controlled trial) OR Topic=(controlled clinical trial OR controlled trial OR clinical trial OR placebo)
6.4 or 5
7.Topic=(human*)
8.6 and 7
9.3 and 8

PubMed [www.ncbi.nlm.nih.gov/sites/entrez/] (searched 10 Sept 2009) (added to PubMed in the last 90 days)

#1 oxime* or hydroxyimin* or ketoxime* or Acetaldoxime* or Aldoxime* or Alloxime* or Amidox or Benolizime* or Diiodide* or diclofurime or dimethylglyoxime or Diacetyl Oxime* or Enviroxime* or Heterocyclic Oxime* or Hydroxyimine* or Hexamethylenedicarbamic Acid or Hydroxyiminomethylpyridinium Dichloride or uvoxamine or methylenebis or Obidoxime* or Pralidoxime* or Pyrimidoxime* or Salicylaldoxime* or Teboroxime* or technetium or trimedoxime or upenazime* or uvoxamine or viroxime* or Zinviroxime*
#2 organopyrophosphate* or organophos* or organothiophos* or OP

#3 (("Phosphoric Acid Esters/adverse effects"[Mesh] OR "Phosphoric Acid Esters/poisoning"[Mesh])) OR ("Organophosphorus Compounds/adverse effects"[Mesh] OR "Organophosphorus Compounds/poisoning"[Mesh] OR "Insecticides"[Mesh])
#4 #2 OR #3
#5 #1 AND #4
#6 ((randomized controlled trial[pt] OR controlled clinical trial[pt]) OR (randomized OR randomised OR randomly OR placebo[tiab]) OR (trial[ti]) OR ("Clinical Trials as Topic"[MeSH Major Topic])) NOT (("Animals"[Mesh]) NOT ("Humans"[Mesh] AND "Animals"[Mesh]))
#7 #5 AND #6

Appendix 2. Searching other resources

Internet searching

www.google.com and www.Clinicaltrials.gov were searched using the keywords 'organophosphate', 'oxime', and 'trial'.

Chinese language databases

CNKI www.cnki.net and WANGFANG www.wangfang.com were searched for Chinese articles (using the terms 'oxime' and OP in the title and limiting to human body trials.) The search terms in Chinese characters are shown in Figure 1, along with the Chinese titles of the articles found. Two further clinical trials that were probably randomised were identified.

Figure 1. Chinese character search strategy and titles of included and excluded articles.

Search strategy characters: 在文章的标题中找"有机磷"AND "解磷定"，发表时间不限。

Included studies:

Zhu 2006 - 朱振远。氯解磷定的早期联合用药与量效分析。中国急救医学 2006，26：939 - 940。

Gu 2008 - 顾慧珍，刘素芝，金文扬，朱蔚，朱海勇，杨进，秦杰。氯解磷定三种不同使用方法在急性有机磷农药中毒救治中的对比。中国急救医学 2008，28：110 - 112。

Excluded studies:

Li 2009- 李伯军，杨光明。大剂量氯磷定持续静脉泵入治疗有机磷中毒 33 例疗效评估。中国实用医药 2009，4：181-2。

Yang 2009- 杨世海，陈彦萍，陆跃伟。反复长程应用氯解磷定治疗急性有机磷农药中毒疗效观察。中国乡村医药杂志 2009，16：63 - 65。

Hu 2008 - 胡男彬，张建军。反复足量使用氯解磷定对胆碱酯酶活力疗效分析。中国现代医生 2008，46：152。

Guo 2008 - 郭清晓，吴金海，赵璟，赵文轩。不同剂量氯解磷定延迟应用治疗 55 例甲拌磷中毒的临床疗效。中华实用诊断与治疗杂志 2008, 22：712 - 713。

Yuan 2003 - 袁茂祥，朱孝华。大剂量氯解磷定救治急性有机磷农药中毒体会。江苏大学学报(医学版)2003,13 ：147-8。

Li 2003 - 李正业，黄嵩，李日勋，陈霞，曾波，倪晓。解磷定持续静滴治疗重度有机磷农药中毒的疗效观察。泸州医学院学报 2003，26：538。

Zhang 2005 - 张舟，李茂琴。解磷定对急性有机磷中毒呼吸衰竭患者的影响。中国急救医学 2005，25：461 - 462。

Zhang 2003 - 张淑敏，程卜林，商桂芬。解磷定两种静脉给药方法的对比研究。齐鲁护理杂志 2003，9：883 - 884。

Cheng 2005 - 程国春。解磷注射液氯磷定治疗急性有机磷农药中毒。医药论坛杂志 2005，26：36 - 37。

Tang 2005 - 唐建林。解磷注射液治疗急性有机磷农药中毒的疗效分析。医学文选 2005 ，24：343-4。

Duan 2006 - 段肖亮，谢鹏飞。氯磷定突击疗法治疗急性有机磷农药中毒患者。中华急诊医学杂志 2006，15：649-50。

Yue 2007- 岳蓉，伏军贤，刘雅东，汪占祥。突击量氯磷定救治重度有机磷中毒临床观察。实用医技杂志 2007;14：1461-3

Zheng 2000 - 郑功泉，宋尚明，李明秀，陈善宏，崔宝文，任大利。突击量氯磷定治疗急性有机磷农药中毒致呼吸肌麻痹 76 例观察。中华内科杂志 2000，39: 655-658。

Kou 2008 - 寇品娟，赵菊萍。应用不同剂量氯磷定治疗重度有机磷农药中毒并发呼吸衰竭 30 例分析。陕西医学杂志 2008，37：1253 - 1254。

WHAT'S NEW

Last assessed as up-to-date: 9 September 2009.

Date	Event	Description
20 December 2010	New citation required but conclusions have not changed	The search was updated to 10 September 2009 and was broadened to include Chinese language trials. Four new studies have been added. The text has been completely revised. Risk of bias and summary of findings tables have been added to comply with new Cochrane guidance. The authors have changed

HISTORY

Protocol first published: Issue 1, 2005

Review first published: Issue 1, 2005

Date	Event	Description
11 July 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

For versions up to 2010, ME & NB screened citations for eligibility, obtained references, contacted authors, extracted data, entered data and wrote the first draft of the review. Ladislaus Szinicz wrote the discussion of pathophysiological explanations for possible lack of efficacy of oximes in humans.

From 2010, ME & NB obtained references, contacted authors, entered data and wrote the first draft of the review. YL, MB & JR screened citations for eligibility, rated articles and extracted data. YL was responsible for the search and rating of the articles in Chinese. All authors approved the final version.

DECLARATIONS OF INTEREST

Two of the authors (ME & NB) are authors on one of the studies.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Wellcome Trust Career Development Fellowship GR063560MA, UK.
- Wellcome Trust/NHMRC International Collaborative Research Grant GR071669MA, Australia.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The methods followed in this review have been updated since the publication of the protocol for this review to reflect revised guidance from The Cochrane Collaboration (Higgins 2008). Thus we used risk of bias assessment rather than the Jadad scale and Schulz assessment of the effectiveness of allocation concealment. We also incorporated a GRADE summary of findings assessment. These changes in methods have not altered the conclusions about the strength of evidence from the studies included in the 2005 version.

The search of Chinese language publications also was added in the 2010 version.

NOTES

The Cochrane Injuries Group and Cochrane Neuromuscular Diseases Group have dual editorial responsibility for this review.

INDEX TERMS

Medical Subject Headings (MeSH)

Antidotes [*therapeutic use]; Cholinesterase Reactivators [therapeutic use]; Organophosphorus Compounds [*poisoning]; Oximes [*therapeutic use]; Pesticides [*poisoning]; Poisoning [drug therapy]; Pralidoxime Compounds [therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans