PROPOSAL FOR THE INCLUSION OF PRALIDOXIME (FOR CHILDREN) IN THE WHO MODEL LIST OF ESSENTIAL MEDICINES

REPORT

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1. **Summary statement of the proposal**

Pralidoxime is proposed for the inclusion in the World Health Organization (WHO) Model List of Essential Medicines for the treatment of acute organophosphorus poisoning in children.

2. **Name of focal point in WHO submitting or supporting the application**

3. **Name of the organisation preparing the application**

Discipline of Clinical Pharmacology, School of Medicine and Public Health, Faculty of Health, University of Newcastle, Level 5, Clinical Sciences Building, NM2, Calvary Mater Hospital, Edith Street, Waratah, 2298, New South Wales, Australia.

4. **International Nonpropriety Name (INN, generic name) of the medicine**

Pralidoxime

5. **Formulation proposed for inclusion**

Injection or oral preparation: formulation not specified

Includes the use of pralidoxime chloride, pralidoxime iodide, pralidoxime mesilate and pralidoxime methylsulfate.

Includes the use of pralidoxime and pralidoxime/atropine combination products supplied as auto-injectors for use by emergency responders.

6. **International availability**

Four different pralidoxime salts are currently commercially available; pralidoxime mesilate/ pralidoxime metilsulfate (Contrathion®), pralidoxime iodide and pralidoxime chloride (Protopam®). Pralidoxime chloride is also available in fixed dose combination products with atropine (Duodote® and ATNAA®). A detailed list of manufacturers and distributors is presented in Appendix A.

7. **Whether listing is requested as an individual medicine or as an example of a therapeutic group**

Listing is requested on the Model List of Essential Medicines as an individual medicine.

8. **Information supporting the public health relevance**

8.1 **Disease burden**

There is currently insufficient information available in the medical literature to derive regional or global estimates of the incidence of acute organophosphorus poisoning in children.

The mortality associated with acute organophosphorus poisoning in adults is typically due to the intentional ingestion (ie suicide attempt) of organophosphate pesticide (Eddleston *et al* 2008). The scale of this issue can be observed in the estimated global and regional incidence of pesticide-related suicides (including organophosphates) presented in Table 1. These estimates represent the number of completed suicides and it is likely that the number of suicide-attempts (with accompanying morbidity) is
substantially higher. These estimates also do not address the morbidity and mortality associated with accidental or occupational exposure to pesticides.

Table 1: Global and regional estimates of pesticide suicides each year

<table>
<thead>
<tr>
<th>Region</th>
<th>Total suicides</th>
<th>Pesticide suicides (% of all suicides)</th>
<th>Plausible range of pesticide suicides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>34,000</td>
<td>7,800 (22.9)</td>
<td>5,200 to 21,910</td>
</tr>
<tr>
<td>Americas</td>
<td>63,000</td>
<td>3,105 (4.9)</td>
<td>1,974 to 8,715</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>34,000</td>
<td>5,629 (16.5)</td>
<td>4,501 to 7,022</td>
</tr>
<tr>
<td>Europe</td>
<td>163,000</td>
<td>6,080 (3.7)</td>
<td>1,872 to 9,170</td>
</tr>
<tr>
<td>South East Asia</td>
<td>246,000</td>
<td>51,050 (20.7)</td>
<td>47,720 to 82,680</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>331,000</td>
<td>184,570 (55.8)</td>
<td>172,730 to 196,410</td>
</tr>
<tr>
<td>Global</td>
<td>873,000</td>
<td>258,234 (30%)</td>
<td>233,997 (27%) to 325,907 (37%)</td>
</tr>
</tbody>
</table>

Source: Gunnell et al (2007)

The global and regional estimates of pesticide suicides were calculated as part of a systematic review conducted by Gunnell et al (2007). The authors estimated that 258,234 deaths per year were associated with pesticide self-poisoning worldwide. It can be observed in Table 1 that the incidence of pesticide poisoning fluctuated between regions with Africa, South East Asia and the Western Pacific having the highest number of pesticide suicides relative to the total number of suicides. The authors of the review suggested that the pattern of pesticide suicides appeared to correspond with the general accessibility of pesticides in each region.

Compared to adults it is more likely that acute poisoning in children is due to accidental exposure to organophosphates. However it appears reasonable to assume that as children reach adolescence an increasing proportion of organophosphorus poisoning cases may be due to attempted suicide rather than unintentional exposure.

It seems likely that the global distribution of organophosphorus poisoning in children will follow a similar pattern to adults due to the accessibility of organophosphorus pesticides.

8.2 Current treatments

The toxicity of organophosphorus compounds is primarily due to inhibition of cholinesterase (by phosphorylation) with consequent accumulation of acetylcholine at nicotinic and muscarinic receptors in the peripheral and central nervous systems (Johnson et al 2000).

Atropine is typically used to alleviate the features of organophosphorus poisoning associated with stimulation of muscarinic receptors including diarrhoea, urinary frequency, miosis, bradycardia, bronchorrhea and bronchoconstriction, emesis, lacrimation, salivation and hypotension (Roberts and Aaron 2007). Atropine acts by competitively blocking acetylcholine at muscarinic receptor sites (Johnson et al 2000).

Oximes (pralidoxime or obidoxime) are used in a complementary role to atropine to treat features associated with stimulation of the nicotinic receptors including muscle fasciculations, progressive muscle weakness (which may lead to paralysis and peripherally-mediated respiratory failure), tachycardia, and hypertension (Roberts and Aaron 2007). Oximes operate by reactivating phosphorylated cholinesterase and forming inert complexes with the residual organophosphorus compound (Johnson et al 2000).
Both atropine and oximes may reduce some of the features associated with acetylcholine accumulation in the central nervous system such as altered consciousness, centrally-mediated respiratory failure and seizures (Roberts and Aaron 2007).

Supportive care measures are also required to manage the symptoms of organophosphorus poisoning including; mechanical ventilation for respiratory failure and benzodiazepines for seizures.

Additionally, decontamination measures such as gastric lavage and administration of activated charcoal are sometimes used in clinical practice. The effectiveness of these interventions in organophosphorus poisoning is unclear (Roberts and Aaron 2007).

8.3 Treatment guidelines

The clinical management of patients with acute organophosphorus poisoning is outlined in Figure 1. The clinical pathway was adapted from a review by Roberts and Aaron (2007).

*Intermediate syndrome:* A minority of patients that appear to be improving after therapy can suddenly develop a profound weakness in neck and respiratory muscles potentially leading to respiratory failure. It has been suggested that patients should be carefully monitored for a few days following apparent recovery to enable the rapid detection and management of intermediate syndrome (Roberts and Aaron, 2007).
Figure 1  Clinical pathway for the management of patients with acute organophosphorus poisoning

Source: Roberts and Aaron (2007)
*Patients may have variable degrees of miosis, salivation, diaphoresis, urinary frequency, or lacrimation, which may assist in diagnosis of organophosphorus poisoning. Because these manifestations are not considered to influence outcome they are not included in this decision tree.
†Assessment of respiratory status includes respiratory rate and depth, presence of adventitious sounds such as rales and rhonchi, presence of bronchorrhoea, and objective measurements of pulse oximetry, arterial blood gases, and forced vital capacity or forced expiratory volume in one second.
‡Muscle weakness: difficulty in mobilisation or reduced forced vital capacity on spirometry before development of paralysis and respiratory failure.
§Caution with patients with a history of exposure to fenthion (or highly fat soluble organophosphorus compounds). Patients with fenthion poisonings are usually characterised by minimal or absent cholinergic symptoms for 24-48 hours, after which they develop increasing muscle weakness and respiratory failure.
9. Treatment details

The dose of pralidoxime commonly recommended in the literature for the treatment of organophosphorus poisoning in adults is a 30 mg/kg bolus, followed by a continuous infusion of 8 mg/kg/hr (Buckley et al 2005). This dose is used to rapidly achieve and maintain a concentration of pralidoxime above 4 mg/L. This is sometimes referred to as the WHO recommended dose (Eddleston et al 2002, Buckley et al 2005).

The recommended dose of pralidoxime is based on the chloride salt; doses for other pralidoxime salts (iodide, mesilate and metilsulfate) are calculated by converting the recommended pralidoxime chloride dose into equivalent dosing units (see Table 2). Some authors have expressed concern about the amount of pralidoxime iodide required to achieve the recommended target as high levels of iodide may increase the risk of thyroid toxicity (Eddleston et al 2008).

### Table 2: Equivalent dosing units of pralidoxime salts

<table>
<thead>
<tr>
<th>Salt</th>
<th>Equivalent dose (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pralidoxime chloride</td>
<td>1</td>
</tr>
<tr>
<td>Pralidoxime mesilate</td>
<td>1.34</td>
</tr>
<tr>
<td>Pralidoxime metilsulfate</td>
<td>1.43</td>
</tr>
<tr>
<td>Pralidoxime iodide</td>
<td>1.53</td>
</tr>
</tbody>
</table>

Source: WHO draft pralidoxime drug monograph (unpublished)

A small case series (n = 7) by Farrer et al (1990) evaluated the commonly recommended dose of 25-50 mg/kg IV pralidoxime for children. However after the initial recommended dose the investigators used a continuous infusion of pralidoxime at 10-20 mg/kg/hr instead of intermittent dosing to alleviate symptoms. All patients in the study appear to have recovered from organophosphorus poisoning. The investigators reported that one patient may have experienced adverse events associated with pralidoxime administration. Based on their clinical experience the authors recommended using continuous infusion dosing in children.

Another study by the same group (Schexnayder et al 1998) examined the pharmacokinetics of pralidoxime 15-50 mg/kg IV, followed by a continuous infusion of pralidoxime at 10-20 mg/kg/hr for the treatment of organophosphorus/carbamate poisoning in children. The study concluded that the pharmacokinetics of pralidoxime in children were widely variable and differed from those previously reported in adults. However as the steady-state plasma concentrations of pralidoxime were consistently greater than 4 mg/L the study recommended using this dosage regimen in children.

**Paediatrics**

Pralidoxime iodide: 20 to 50 mg/kg as intermittent doses required to alleviate symptoms. An infusion can be used after an initial dose has been given (MIMS® Australia [http://www.mims.com.au](http://www.mims.com.au)).

Pralidoxime chloride: For mild toxicity treat patients with 1 to 2 g orally; repeat in 3 hours if necessary. For moderate to severe toxicity, patients can receive intermittent dosing (25 to 50 mg/kg IV; repeat in 1 to 2 hours, then at 10 to 12 hour intervals if necessary) or continuous infusion (25 mg/kg IV as single dose, then begin infusion at 10 to 20 mg/kg/hr) (DRUGDEX® drug evaluations [www.micromedex.com](http://www.micromedex.com)).

A review of the literature did not identify any dosing information for the use of pralidoxime metilsulfate or pralidoxime mesilate in children.
10. Identification of clinical evidence

Searches were conducted in the databases indicated in Table 3. The search terms included the following:

- Pralidoxime iodide, pralidoxime chloride, pralidoxime mesilate, Contrathon®, Protopam®

Table 3: Electronic databases searched during the review of pralidoxime

<table>
<thead>
<tr>
<th>Database</th>
<th>Date Searched</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEDLINE and EMBASE&lt;sup&gt;a&lt;/sup&gt;</td>
<td>16 May 2008</td>
</tr>
<tr>
<td>Cochrane library</td>
<td>16 May 2008</td>
</tr>
<tr>
<td>PREMEDLINE&lt;sup&gt;b&lt;/sup&gt;</td>
<td>16 May 2008</td>
</tr>
</tbody>
</table>

<sup>a</sup> Using the EMBASE.com interface  
<sup>b</sup> Using the PubMed interface

Comprehensive details of the literature searches performed using the electronic databases are presented in Appendix B. The citation lists of included studies were searched to identify any additional studies.

Studies were included for review if they were systematic reviews, randomised controlled trials (RCTs) or non-randomised comparative trials evaluating the effectiveness of pralidoxime for the treatment of organophosphorus poisoning in children.

In the absence of studies in children, evidence regarding the effectiveness of pralidoxime in adults was assessed.

11. Summary of comparative effectiveness in a variety of clinical settings

11.1 Summary of available efficacy data

No comparative evidence was identified regarding the effectiveness of pralidoxime in children.


The literature search identified one RCT that was published after the systematic reviews were conducted (Pawar et al 2006).

An additional RCT was also identified, however this study has only recently been completed and the results are not yet published (ISRCTN55264358, www.controlled-trials.com).

Systematic reviews

The characteristics of the included systematic reviews are presented in Appendix C.

The systematic review by Buckley et al 2005 (Cochrane review) was an update of the earlier review by Eddleston et al 2002.
Two systematic reviews were identified as high quality (Buckley et al 2005, Rahimi et al 2006). Another review conducted by Peter et al (2006) was regarded as providing medium quality evidence as some of the details of the literature review/data extraction procedures were unclear. The reviews by Eddleston et al (2002) and Bairy et al (2006) were classified as low-quality due to inadequate reporting of systematic review procedures.

Two reviews took a meta-analytic approach and combined data from RCTs with data from non-randomised studies (Peter et al 2006, Rahimi et al 2006). However the use of non-randomised studies in these analyses may have limited the validity of the results.

The results and conclusions of each systematic review are presented in Table 4. A summary of each of the studies included in the systematic reviews is shown in Table 5. Details of these studies were extracted from summary tables of the included systematic reviews, abstracts of published articles or direct from the publication when available (Chugh et al 2005, Cherian et al 2005). An additional study was identified in a number of systematic reviews (Dadan et al 1999), however this study was only in abstract form and was not analysed in the systematic reviews.

Table 4: Results of systematic reviews assessing the comparative effectiveness of pralidoxime

<table>
<thead>
<tr>
<th>Systematic review (year)</th>
<th>Results/conclusions</th>
</tr>
</thead>
</table>
  **Conclusion:** A generalised statement that pralidoxime should not be used in OP poisoning is not supported by the published results |
  **Conclusion:** Current evidence is insufficient to indicate whether oximes are harmful or beneficial in the management of acute organophosphorus pesticide poisoning |
  **Conclusion:** The clinical benefits of oximes in OP poisoning remains unclear |
  ○ Oxime therapy was not associated with a statistically significant difference in mortality (RD 0.09, 95% CI -0.08, 0.27); need for mechanical ventilation (RD 0.16, 95% CI -0.07, 0.38), incidence of intermediate syndrome (RD 0.16, 95% CI -0.12, 0.45) compared to standard care.  
  ○ Oxime therapy was associated with a statistically significant increase in the need for intensive care (RD 0.19, 95% CI 0.01, 0.36) compared to standard care  
  **Conclusion:** Based on the current available data on human organophosphate poisoning, oxime therapy was associated with either a null effect or possible harm |
  ○ Oxime therapy was associated with a statistically significant increase in mortality (RR 2.17, 95% CI 1.34, 3.51); need for mechanical ventilation (RR 1.53, 95% CI 1.16, 2.02), incidence of intermediate syndrome (RR 1.57, |
WHO EML – pralidoxime – June 2008

Systematic review (year) | Results/conclusions
--- | ---
 | 95% CI 1.11, 2.11) compared to standard care.
**Conclusion:** Oximes are not effective in the management of organophosphate-poisoned patients and can worsen the patient's clinical situation

Table 5: Characteristics/results of studies included in the systematic reviews

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Interventions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duval (1991)</td>
<td>Retrospective comparison (N = 62)</td>
<td>Pralidoxime (1200 mg/24 hr) vs standard treatment</td>
<td>No statistical difference in the risk of death or the need for ventilation between the treatment groups</td>
</tr>
<tr>
<td>De Silva (1992)</td>
<td>Historical comparison (N = 45)</td>
<td>Pralidoxime (4 g over first 24 hr then 1 g/day) vs historical control</td>
<td>No statistical difference in the risk of death, the need for ventilation or the rate of intermediate syndrome between the treatment groups</td>
</tr>
<tr>
<td>Abdollahi (1995)</td>
<td>Retrospective comparison (N = 34)</td>
<td>Pralidoxime (600-800 mg every 4-8 hrs, based on patient condition) vs standard treatment</td>
<td>No statistical difference in the risk of death or the need for ventilation between the treatment groups</td>
</tr>
<tr>
<td>Samuel (1995)</td>
<td>RCT (N = 72)</td>
<td>High dose pralidoxime (12 g reducing infusion over 4 days) vs low dose pralidoxime (1 g bolus)</td>
<td>High dose pralidoxime was associated with a significantly higher risk of death, need for ventilation and rate of intermediate syndrome</td>
</tr>
<tr>
<td>Cherian (1997)</td>
<td>RCT (N = 110)</td>
<td>Pralidoxime (12 g infusion over 3 days) vs placebo (and standard care)</td>
<td>Pralidoxime was associated with a significantly higher risk of death, need for ventilation and rate of intermediate syndrome</td>
</tr>
<tr>
<td>Balali-Mood (1998)</td>
<td>Prospective comparison (N = 72)</td>
<td>Pralidoxime (14 ± 7.4 g), obidoxime (60.6 ± 24.3 g) vs standard treatment</td>
<td>Pralidoxime and obidoxime were associated with more respiratory complications. No deaths were observed in the pralidoxime arm. Deaths were observed in the obidoxime and standard care arms</td>
</tr>
<tr>
<td>Sungur (2001)</td>
<td>Retrospective comparison (N = 47)</td>
<td>Pralidoxime (3.5 ± 3.0 g) vs standard treatment</td>
<td>No statistical difference in the risk of death between the treatment groups</td>
</tr>
<tr>
<td>Cherian (2005)</td>
<td>RCT (N = 21)</td>
<td>Pralidoxime (12 g/day (severe) or 4 g/day (moderate) over 3 days) vs placebo (and standard care)</td>
<td>No statistical difference in the risk of death or the need for ventilation between the treatment groups</td>
</tr>
<tr>
<td>Chugh (2005)</td>
<td>Prospective comparison (N = 30)</td>
<td>Pralidoxime (1 g/6 hrs) vs standard treatment</td>
<td>No statistical difference in the risk of death or the need for ventilation between the treatment groups</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RD, risk difference; RR, relative risk.

The studies included in the systematic reviews suggest pralidoxime was associated with either a null affect or possible harm.

The systematic reviews all acknowledged the limitations of the current evidence base (primarily the small sample size, poor methodology and inadequate reporting). Eddleston et al (2002), Buckley et al (2005) and Bairy et al (2005) indicated that the current evidence is too weak to draw conclusions. However Peter et al (2005) and
Rahimi et al (2005) conclude that even with the limitations, the current evidence indicates that pralidoxime is not effective in the treatment of organophosphate poisoning.

In addition to the methodological limitations of the reviewed studies a number of other issues were identified in the systematic reviews.

**Oxime dosage**

The dosages of pralidoxime used in most of the studies would have been unlikely to achieve and/or maintain the WHO recommended target (pralidoxime serum concentrations above 4 mg/L). The review by Peter et al (2006) questioned the relevance of achieving this therapeutic threshold as this dose was calculated based on animal studies, studies in healthy volunteers and a limited number of organophosphorus poisoning case studies.

The RCT by Samuel et al (1995) is noteworthy as it reported a lower mortality rate with pralidoxime given as a single 1 g bolus (low-dose) compared with 12 g given as a reducing infusion without a loading dose (high-dose). The reviews by Eddleston et al (2002), Buckley et al (2005) and Bairy et al (2006) suggest that this could be interpreted as the bolus dose achieving a therapeutic concentration for a limited amount of time. However the reviews by Peter et al (2006) and Rahimi et al (2006) propose that the increased mortality seen in the ‘high-dose’ arm suggest that the ineffectiveness of oximes observed in studies is not due to insufficient dose.

**Therapeutic timeframe**

The lack of efficacy with pralidoxime treatment may have been partially due to the time to treatment initiation and the type of organophosphorus compound involved in the poisoning.

Organophosphorus compounds exhibit their toxic affect by phosphorylating the cholinesterase enzyme. The phosphorylated cholinesterase is thought to 'age' (the chemical reaction becomes irreversible) and therefore becomes resistant to reactivation by pralidoxime over time. This limits the timeframe in which therapeutic intervention with pralidoxime is likely to be clinically useful.

Pharmacokinetic studies have also indicated that dimethyl and diethyl organophosphorus compounds might have different ageing kinetics. It is believed that dimethyl organophosphate compounds ‘age’ considerably faster than diethyl compounds. Therefore the timeframe for therapeutic intervention (i.e before the phosphorylated cholinesterase has ‘aged’) is considerably smaller with dimethyl compounds.

**Toxic load**

The review by Peter et al (2006) raised the issue that pralidoxime (even at optimal plasma concentrations) may be unable to counteract ‘megadose’ concentrations of organophosphorus compounds. This hypothesis was based on an earlier case series by Willems et al (1993), which indicated that the therapeutic effect of pralidoxime was dependent on both the therapeutic concentrations of pralidoxime as well as the organophosphorus compound. Willems et al (1993) observed that no enzyme reaction
occurred with pralidoxime treatment while ethyl and methyl parathion (an organophosphate) concentration remained above 30 mcg/mL. The review by Peter et al (2006) did not attempt to define a ‘megadose’. The majority of patients enrolled in the included studies experienced organophosphate poisoning as a result of attempted suicide and therefore it is possible that a proportion of these patients ingested a ‘megadose’ of organophosphorus compounds.

Toxicity of the antidote

The reviews by Peter et al (2006) and Rahimi et al (2006) both raised the issue that the trend against pralidoxime observed in the RCTs may have been due to the toxicity of pralidoxime. In particular Peter et al (2006) discussed the potential of pralidoxime to form stable phosphoryl oximes (POX) compounds during treatment. POX compounds, similarly to organophosphates, exhibit high anticholinesterase activity and can potentially result in a transient neuromuscular blockade. Peter et al (2006) suggested that this effect may be partially responsible for the variable response of patients to pralidoxime therapy.

Randomised controlled trials

The literature search identified one RCT that was published after the systematic reviews were conducted (Pawar et al 2006).

In a prospective, randomised, single-centre, open-label trial by Pawar et al (2006); 200 patients were randomly allocated to receive ‘low-dose’ pralidoxime iodide (2 g loading dose, infusion of 1 g over 1 hour every 4 hours) or ‘high-dose’ pralidoxime iodide (2 g loading dose, infusion of 1 g over 1 hour every hour). Neither dose represented the WHO recommended regimen (30 mg/kg bolus, followed by a continuous infusion of 8 mg/kg/hr); however it is likely that the ‘high-dose’ treatment arm would have maintained pralidoxime serum concentrations above 4 mg/L (WHO recommended target). Patients were excluded from the study if they were < 12 years of age, had a chronic disease or malignancy, presented later than 24 hours after ingestion, failed to be resuscitated successfully or were asymptomatic in regards to organophosphorus poisoning. The authors suggested that the included patient group represented moderately severe cases of organophosphate poisoning. The applicability of the results of this study to patients with different degrees of organophosphate poisoning is unclear.

None of the eligible patients refused to participate in the trial. All patients were able to purchase the required medication for the trial, which the authors claimed cost approximately US$400 for the first 48 hours.

The study also reported on the characteristics of organophosphorus poisoning, including the type of organophosphorus compound, the time to admission and the quantity of poison consumed (ie toxic load) (summarised in
Table 6).
Table 6: Characteristics of organophosphorus poisoning for the comparison between ‘low-dose’ and ‘high-dose’ pralidoxime (Pawar et al 2006)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>‘Low-dose’ pralidoxime n = 100</th>
<th>‘High-dose’ pralidoxime n = 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingestion of diethyl pesticides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- chlorpyrifos</td>
<td>40</td>
<td>22</td>
</tr>
<tr>
<td>- quinalphos</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Ingestion of dimethyl pesticides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- dimethoate</td>
<td>45</td>
<td>65</td>
</tr>
<tr>
<td>- monocrotophos</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>- methyl parathion</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>- malathion</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>- fenitrothion</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Median (IQR) time between ingestion and admission (min)</td>
<td>112.5 (60.0-150.0)</td>
<td>120.0 (90.0-142.5)</td>
</tr>
<tr>
<td>Median (IQR) quantity of poison consumed (mL)</td>
<td>15 (10-20)</td>
<td>15 (15-20)</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range

There were significant differences in the type of organophosphate consumed with more patients in the ‘low-dose’ arm ingesting diethyl pesticides (primarily chlorpyrifos), while more patients in the ‘high-dose’ arm ingested dimethyl pesticides (primarily dimethoate). The authors have interpreted the differences in organophosphorus consumption as a bias against the ‘high-dose’ pralidoxime treatment arm. This bias (ie the rapid ‘ageing’ affect associated with dimethyl compounds) may have been reduced by the short time between the poisoning event and treatment.

The study reported a median time from ingestion to admission of approximately two hours. Correspondence regarding this article (Pawar et al 2007), indicated that this time did not correspond to the time of treatment initiation. However the longest time between ingestion and treatment was 7.5 hours. It is unclear whether the time to admission/time to treatment initiation is representative of clinical practice.

The study claimed to have been able to determine the quantity of poison consumed. However as highlighted in correspondence from Goel et al (2007) this is extremely difficult to assess in clinical practice. It is unclear whether the median quantity of poison consumed reported in the study provides a meaningful measure of poison load.
Table 7 summarises the results of the comparison between ‘low-dose’ pralidoxime and ‘high-dose’ pralidoxime reported in Pawar et al (2006). The primary outcomes of this study were: median atropine dose in the first 24 hours of admission, proportion of patients requiring intubation and the number of days on ventilation.
Table 7: Summary of results of the comparison between ‘low-dose’ and ‘high-dose’ pralidoxime (Pawar et al 2006)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>‘Low-dose’ pralidoxime n = 100</th>
<th>‘High-dose’ pralidoxime n = 100</th>
<th>Difference or relative risk (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median days ventilated&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10 (8, 12)</td>
<td>5 (4, 5)</td>
<td>5 (5, 6)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Median atropine dose in first 24 hr (mg)</td>
<td>30 (25, 45)</td>
<td>6 (4, 6)</td>
<td>24 (24, 26)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Neck muscle weakness</td>
<td>94%</td>
<td>80%</td>
<td>0.85 (0.76, 0.95)</td>
<td>0.0054</td>
</tr>
<tr>
<td>Intubated during admission</td>
<td>88%</td>
<td>64%</td>
<td>0.72 (0.62, 0.86)</td>
<td>0.0001</td>
</tr>
<tr>
<td>- Intubated after randomisation</td>
<td>19/31 (61.3%)</td>
<td>1/37 (2.7%)</td>
<td>0.044 (0.063, 0.31)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Deaths</td>
<td>8%</td>
<td>1%</td>
<td>0.13 (0.016, 0.98)</td>
<td>0.0349</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>35%</td>
<td>8%</td>
<td>0.23 (0.11, 0.47)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Mean systolic blood pressure in first 24 hr (mm Hg)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>115.4 (SD 6.10)</td>
<td>136.2 (SD 4.97)</td>
<td>20.6 (19.0, 22.2)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Mean diastolic blood pressure in first 24 hr (mm Hg)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>75.6 (SD 4.96)</td>
<td>84.1 (SD 2.56)</td>
<td>8.3 (7.2, 9.5)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Abbreviations: SD, standard deviation
Note: All statistical analysis based on unadjusted values
<sup>a</sup> ‘low-dose’ pralidoxime (n = 80); ‘high-dose’ pralidoxime (n = 63)
<sup>b</sup> ‘low-dose’ pralidoxime (n = 97); ‘high-dose’ pralidoxime (n = 99)

‘High-dose’ pralidoxime significantly reduced the number of deaths and the number of patients with pneumonia compared to the ‘low-dose’ treatment arm. Outcomes associated with the administration of supportive therapy (median atropine dose in first 24 hr of admission, proportion of patients requiring intubation and the number of days on ventilation) were also significantly improved in the ‘high-dose’ arm.

Correspondence related to this study suggested that the atropine dose used in the first 24 hours appeared to be lower than expected for moderately severe organophosphate poisoning (Goel et al 2007, Peter et al 2007, Joshi and Kalantri 2007). In further correspondence Pawar (2007) clarified the reason for the lower atropine dose (different atropinisation endpoints), however the clinical significance of the lower dose remains unclear.

The trial claimed that no substantial adverse events were experienced by patients enrolled in the trial. However, the authors of the study did acknowledge an increase in blood pressure (both systolic and diastolic) in the ‘high-dose’ arm compared with the ‘low-dose’ treatment arm.

### 11.2 Summary of available safety data

An observational study conducted by Quail et al (2007) reviewed the current data relating to the safety of pralidoxime treatment in children. This study consisted of two components; a review of case studies published between 2001-2004 and a review of data from the Toxic Exposure Surveillance System (TESS) between 1999-2001. Patients were included in the analysis if they were children (< 16 years of age) who had been treated with pralidoxime and were residents of the United States.
No information regarding the toxicity of pralidoxime in children was identified in the literature search. The review of the TESS database identified 81 patients that met the inclusion criteria. Three children (3.7%) developed an adverse event that was coded as associated with treatment and two patients (2.5%) died in association with pralidoxime administration. The case abstracts of these five patients were further reviewed by Quail and colleagues. The authors of the study considered that these adverse events were unlikely to be related to pralidoxime administration.

The safety data presented in the Australian product information (www.mims.com.au) indicates that:

- Pralidoxime administration may be associated with drowsiness, dizziness, disturbances of vision, nausea, tachycardia, headache, hyperventilation and muscular weakness.
- Large doses of pralidoxime may cause transient neuromuscular blockade.
- Intravenous infusion of pralidoxime should be conducted slowly as tachycardia, laryngospasm and muscle rigidity have been attributed to administering pralidoxime at too rapid a rate.
- Excitement and manic behaviour immediately following recovery of consciousness have been reported in several cases. However, similar behaviour has occurred in cases of organophosphate poisoning that were not treated with pralidoxime.
- When atropine and pralidoxime are used together, the signs of atropinisation may occur earlier than might be expected when atropine is used alone.

11.3 Discussion

In summary, previous systematic reviews have not been able to establish the efficacy of pralidoxime in the treatment of organophosphorus poisoning in adults. Additional data from a recent RCT appears to support the benefit of ‘high-dose’ pralidoxime treatment; however the generalisability of these results to other clinical situations is unclear. Some of the uncertainty regarding the efficacy of pralidoxime may be addressed when the results of a recently completed large RCT conducted in Sri Lanka are published.

There is no relevant comparative data in children and the efficacy of pralidoxime treatment appears to be inferred from the adult studies. However it is noteworthy that a small study (which recommended pralidoxime treatment) observed that the pharmacokinetics of pralidoxime in children were widely variable and differed from those previously reported in adults.

Further research is required to adequately evaluate the toxicity of pralidoxime treatment in children.
12. Summary of available data on comparative cost and cost effectiveness within the pharmacological class or therapeutic group

12.1 Global costs of pralidoxime


Pralidoxime Iodide Pack: 25 mg /1 mL, 20 mL (5 vials): $329.42

*United States pricing details* ([www.ecomm.baxter.com](http://www.ecomm.baxter.com)) – (US dollars)

Pralidoxime Chloride Pack: 1 g, 20 mL (6 vials): $520.20

A review of the literature did not identify any costing information for either pralidoxime metilsulfate or pralidoxime mesilate.

12.2 Cost effectiveness

No studies were identified that examined the cost-effectiveness of pralidoxime for the treatment of organophosphorus poisoning.

13. Summary of regulatory status of the medicine

Pralidoxime is currently marketed worldwide and may be available in generic form. The regulatory status of the pralidoxime salts (iodide, chloride, mesilate and metilsulfate) in each country is difficult to ascertain but it is likely to vary from country to country. For example, pralidoxime chloride is the only pralidoxime salt approved by the United States Food and Drug Administration (FDA).

The FDA has also approved pralidoxime chloride and pralidoxime chloride/atropine auto-injectors for the emergency treatment of organophosphorus poisoning, nerve agent toxicity and overdosage by anticholinesterase drugs ([www.fda.gov](http://www.fda.gov)).

14. Availability of pharmacopoeial standards

From MARTINDALE® database ([www.micromedex.com](http://www.micromedex.com))

- Pralidoxime chloride: US pharmacopeia
- Pralidoxime iodide: Chinese pharmacopeia
- Pralidoxime metilsulfate: Italian pharmacopeia
- Pralidoxime mesilate: None

15. Proposed text for the WHO Model Formulary


*Indication*

Anticholinergic organophosphorus pesticide and chemical poisoning.

*Contraindications*

Hypersensitivity to pralidoxime.
**Warnings**

Pralidoxime is not effective in the treatment of poisoning due to phosphorus, inorganic phosphates or organophosphates not having anticholinesterase activity.

The use of pralidoxime for the treatment of poisoning of the carbamate class is relatively ineffective. Pralidoxime treatment may lead to increased toxicity with carbamyl poisoning.

**Precautions**

Intravenous infusion of pralidoxime should be carried out slowly as tachycardia, laryngospasm and muscle rigidity have been attributed to administering pralidoxime at too rapid a rate.

Pralidoxime should be used with caution in treating organophosphate overdosage in cases of myasthenia gravis, as it may precipitate a myasthenic crisis.

*Impaired renal function.* Pralidoxime is excreted in the urine, a decrease in renal function will result in increased blood levels of the drug. Therefore, the dosage of pralidoxime should be reduced in the presence of renal insufficiency.

**Adverse reactions**

Drowsiness, dizziness, disturbances of vision, nausea, tachycardia, headache, hyperventilation and muscular weakness have been reported after the use of pralidoxime. Rapid intravenous infusion of pralidoxime has been associated with tachycardia, laryngospasm and muscle rigidity. Large doses of pralidoxime may cause transient neuromuscular blockade.

Excitement and manic behaviour immediately following recovery of consciousness have been reported in several cases. However, similar behaviour has occurred in cases of organophosphate poisoning that were not treated with pralidoxime.

When atropine and pralidoxime are used together, the signs of atropinisation may occur earlier than might be expected when atropine is used alone.

**Dosage and administration**

Treatment of organophosphate poisoning consists of maintaining respiration; administration of atropine and pralidoxime; removal of organophosphates from clothing and skin, and administration of supportive measures.

Pralidoxime administration should be started at the same time as atropine.

Atropine is administered intravenously until signs of mild atropinisation occur and the muscarinic symptoms relieved. Assessing cardiac effects by monitoring heart rate, watching for signs of mydriasis, dry mouth and decreased respiratory symptoms will give a good clinical assessment of atropinisation.

Treatment will be most effective if given within a few hours after poisoning has occurred. Pralidoxime administration more than 48 hours after exposure is unlikely to be effective, however severely poisoned patients have occasionally responded after such an interval.
In severe cases, especially after ingestion of the poison, it may be desirable to monitor the effect of therapy electrocardiographically because of the possibility of heart block due to the anticholinesterase. Where the poison has been ingested, it is particularly important to take into account the likelihood of continuing absorption from the lower bowel, since this constitutes new exposure. In effect, the patient should be titrated with pralidoxime as long as signs of poisoning recur.

If convulsions interfere with respiration, benzodiazepines may be given with care.

*Paediatric dosing*

Pralidoxime iodide: 20 to 50 mg/kg as intermittent doses required to alleviate symptoms. An infusion can be used after an initial dose has been given.

Pralidoxime chloride: For mild toxicity treat patients with 1 to 2 g orally; repeat in 3 hours if necessary. For moderate to severe toxicity, patients can receive intermittent dosing (25 to 50 mg/kg IV; repeat in 1 to 2 hours, then at 10 to 12 hour intervals if necessary) or continuous infusion (25 mg/kg IV as single dose, then begin infusion at 10 to 20 mg/kg/hr).

Doses for pralidoxime mesilate and pralidoxime metilsulfate should be calculated by converting the recommended pralidoxime chloride dose into equivalent dosing units.

*Overdosage*

Administer artificial respiration and other supportive therapy as needed.
Reference List


Appendix A

A review of the DRUGDEX® and MARTINDALE® databases was undertaken to identify international availability of pralidoxime products. In addition a general internet search was performed using the GOOGLE® interface. The international availability of pralidoxime is summarised in Table A. 1.

Table A. 1: International availability of pralidoxime

<table>
<thead>
<tr>
<th>Brand</th>
<th>Active ingredient</th>
<th>Manufacturer/Distributor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contrathion®</td>
<td>Pralidoxime metilsulfate</td>
<td>Aventis (Brazil, Argentina), IFET (Greece), Keymen (Turkey), Sanofi-Aventis (Italy), SERB (France)</td>
</tr>
<tr>
<td>Nerve Agent Antidote L4A1</td>
<td>pralidoxime mesilate, avizafone, atropine sulfate</td>
<td>Ministry of Defence (UK)</td>
</tr>
<tr>
<td>Duodote® or ATNAA®</td>
<td>atropine, pralidoxime chloride&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Meridian (USA), King Pharmaceuticals (USA), Survival Technology (USA)</td>
</tr>
<tr>
<td>Protopam®</td>
<td>pralidoxime chloride</td>
<td>Baxter Healthcare Corporation (USA), Wyeth Pharmaceuticals (USA), Wyeth-Ayerst (Canada, USA)</td>
</tr>
<tr>
<td>-</td>
<td>pralidoxime chloride&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Meridian (USA), King Pharmaceuticals (USA), Survival Technology (USA)</td>
</tr>
<tr>
<td>-</td>
<td>pralidoxime iodide</td>
<td>Phebra (Australia), Troikaa Pharmaceuticals Ltd (India), Trisachem Pharmaceuticals (India)</td>
</tr>
</tbody>
</table>


<sup>a</sup> Auto-injector administration of medication
Appendix B

Search strategies were used to identify relevant studies of pralidoxime for the treatment of organophosphate poisoning. The MEDLINE and EMBASE databases were search using the EMBASE.com interface. The PREMEDLINE database was search using the PUBMED interface. The CDSR, DARE, CENTRAL, CMR, HTA, NHSEED databases were search using the Cochrane library interface. The search results for EMBASE.com are presented in Table B. 1, the results of the Cochrane library are presented in Table B. 2 and the results from PUBMED are presented in Table B. 3.

**Table B. 1: Pralidoxime for acute organophosphate poisoning in children, EMBASE.com search strategy (16th May 2008)**

<table>
<thead>
<tr>
<th>#</th>
<th>Keywords</th>
<th>Results</th>
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<tr>
<td>1</td>
<td>pralidoxime:de</td>
<td>1,818</td>
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<tr>
<td>2</td>
<td>'1 methyl 2 formylpyridinium oxime':ti,ab OR '1 methylpyridinium 2 carbadoxaloxide salt':ti,ab OR '2 pyridinealdoxime methosulfate':ti,ab OR 'n methyl 2 pyridiniumaldoxime':ti,ab OR 'n methylpyridinium 2 aldoxime':ti,ab OR 'n methylpyridinium 2 carbadoxaloxide':ti,ab OR 'pralidoxim':ti,ab OR 'pralidoxime':ti,ab</td>
<td>761</td>
</tr>
<tr>
<td>3</td>
<td>'1 methylpyridinium 2 carbadoxaloxide chloride':ti,ab OR '2 pyridinaldoxime methochloride':ti,ab OR '2 pyridinealdoxime methochloride':ti,ab OR '2 pyridinealdoxime methyl chloride':ti,ab OR '2 pyridinealdoxime methomethyl chloride':ti,ab OR '2 pyridinealdoxime methiodide':ti,ab OR '2 pyridinealdoxime methyl iodide':ti,ab OR 'pralidoxime methochloride':ti,ab OR 'pyridine 2 aldoxime methochloride':ti,ab OR 'pralidoxime hydrochloride':ti,ab OR 'pralidoxime iodide':ti,ab OR 'pyridiniumaldoxime methochloride':ti,ab OR 'pralidoxine chloride':ti,ab</td>
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</tr>
<tr>
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<td>('1 methyl 2 hydroxyiminomethylpyridinium iodide':ti,ab OR '2 (hydroxyiminomethyl) 1 methylpyridinium iodide':ti,ab OR '2 azininaldoxime methiodide':ti,ab OR '2 formyl 1 methylpyridinium iodide oxime':ti,ab OR '2 formyl 1 methylpyridinium iodide':ti,ab OR '2 pyridinaldoximethyl iodide':ti,ab OR '2 pyridinaldoxime methiodide':ti,ab OR '2 pyridinealdoxime methiodide':ti,ab OR '2 pyridinealdoxime methiodide':ti,ab</td>
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</tr>
<tr>
<td>5</td>
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</tr>
<tr>
<td>7</td>
<td>protopam:ti,ab,tn OR contrathion:ti,ab,tn</td>
<td>141</td>
</tr>
<tr>
<td>8</td>
<td>pam:ti,ab OR 2pam:ti,ab OR 2<em>pam:ti,ab OR pam</em>:ti,ab OR 2pam*:ti,ab</td>
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</tr>
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</table>
### Table B. 2: Pralidoxime for acute organophosphate poisoning in children, Cochrane library search strategy (16th May 2008, Issue 2)

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<tbody>
<tr>
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<td>MeSH descriptor Pralidoxime Compounds explode all trees</td>
<td>20</td>
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<tr>
<td>2</td>
<td>pralidoxime[tiab]</td>
<td>27</td>
</tr>
<tr>
<td>3</td>
<td>(protopam or contrathion)</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>(PAM) or (2PAM) or (2<em>PAM) or (PAM</em>) or (2PAM*) or (2<em>PAM</em>) or (P2S)</td>
<td>1938</td>
</tr>
<tr>
<td>5</td>
<td>(organoph*)</td>
<td>243</td>
</tr>
<tr>
<td>6</td>
<td>(#4 AND #5)</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>(#1 OR #2 OR #3 OR #6)</td>
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</tbody>
</table>

### Table B. 3: Pralidoxime for acute organophosphate poisoning in children, Pubmed search strategy (16th May 2008)

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<td>pralidoxime[tiab]</td>
<td>467</td>
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<td>2</td>
<td>protopam[tiab] OR contrathion[tiab]</td>
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<td>4</td>
<td>organophos*[tiab]</td>
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<tr>
<td>5</td>
<td>#3 and #4</td>
<td>175</td>
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<td>6</td>
<td>#1 or #2 or #5</td>
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<tr>
<td>7</td>
<td>Search #1 or #2 or #5 Limits: MEDLINE</td>
<td>565</td>
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<td>8</td>
<td>#6 NOT #7</td>
<td>23</td>
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</table>
Appendix C

Five systematic reviews were identified that assessed the evidence for the use of pralidoxime in the treatment of organophosphorus poisoning. The characteristics of these reviews are summarised in Table C. 1.

Table C. 1: Characteristics of systematic reviews assessing the comparative effectiveness of pralidoxime

<table>
<thead>
<tr>
<th>Systematic review (year)</th>
<th>Search Strategy</th>
<th>Inclusion criteria (included studies)</th>
<th>Methodology</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eddleston (2002)</td>
<td>A literature search was conducted using Medline, Embase and Cochrane databases. Reference lists of included articles were search. Communication with experts to identify unpublished studies. Brief search strategy. Keywords included “organophosphate, poisoning, overdosage, oxime” Literature search conducted in February 2002</td>
<td>Details of the inclusion criteria were not reports (n = 4)</td>
<td>Details of literature review and data extraction procedures were unclear No assessment of quality was undertaken Results were not meta-analysed</td>
<td>Low quality - Inadequate reporting (inclusion criteria, methodology) Limited validity - Included non-randomised studies</td>
</tr>
<tr>
<td>Buckley (2005)</td>
<td>A literature search was conducted using Medline, Embase, UK National Research Register, Injuries Group Specialised Register, Clinicaltrials.gov and Cochrane databases. Reference lists of included articles were search. Communication with experts to identify unpublished studies. Detailed search strategy. Search terms included terms for organophosphorus combined with terms for oximes Literature search conducted in November 2003</td>
<td>Studies with the following characteristics were included: RCT; patients with acute OP poisoning; oxime therapy; reported death, intermediate syndrome or need for mechanical ventilation as outcomes (n = 2)</td>
<td>The literature review and data extraction were completed by two independent reviewers An assessment of quality (randomisation, blinding, allocation concealment) was undertaken Results were not meta-analysed</td>
<td>High quality</td>
</tr>
<tr>
<td>Systematic review (year)</td>
<td>Search Strategy</td>
<td>Inclusion criteria (included studies)</td>
<td>Methodology</td>
<td>Comment</td>
</tr>
<tr>
<td>-------------------------</td>
<td>----------------</td>
<td>--------------------------------------</td>
<td>-------------</td>
<td>---------</td>
</tr>
<tr>
<td>Bairy (2006)</td>
<td>A literature search was conducted using Pubmed, Ovid, Medline and Cochrane databases. Web search using Google interface. Reference lists of included articles were searched. Brief search strategy. Keywords included “organophosphate, poisoning, overdosage, oxime, trial”</td>
<td>Details of the inclusion criteria were not reported (n = 8)</td>
<td>Details of literature review and data extraction procedures were unclear. No assessment of quality was undertaken. Results were not meta-analysed.</td>
<td>Low quality - Inadequate reporting (literature search, inclusion criteria, methodology) Limited validity - Included non-randomised studies</td>
</tr>
<tr>
<td>Peter (2006)</td>
<td>A literature search was conducted using Medline and Toxline databases. Reference lists of included articles were search. Brief search strategy. Keywords included “insecticides, organophosphate, oximes, pralidoxime, poisoning” Literature search conducted in May 2005</td>
<td>Studies with the following characteristics were included: comparative clinical trials (standard care)” patients with acute OP poisoning; oxime therapy; reported death or need for mechanical ventilation as outcomes (n = 7)</td>
<td>Details of literature review and data extraction procedures were unclear. Informal assessment of quality (randomisation, inclusion/exclusion criteria, criteria for intubation, need for intensive care, intention to treat analysis) was undertaken. Meta-analysis conducted using the DerSimonian and Laird method (random effects) Results presented as pooled RD</td>
<td>Medium quality - Inadequate reporting (methodology) Limited validity - Included non-randomised studies</td>
</tr>
<tr>
<td>Systematic review (year)</td>
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<td>Inclusion criteria (included studies)</td>
<td>Methodology</td>
<td>Comment</td>
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<tr>
<td>-------------------------</td>
<td>----------------</td>
<td>--------------------------------------</td>
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</table>
| Rahimi (2006)           | A literature search was conducted using Pubmed, Emtree and Scopus databases. Web search using Google interface Reference lists of included articles were search. Brief search strategy. Keywords included “organophosphate, oxime, clinical trial” Literature search conducted in November 2005 | Studies with the following characteristics were included: comparative clinical trials (standard care); reported death, intermediate syndrome or need for mechanical ventilation as outcomes (n = 6) | The literature review and data extraction were completed by two independent reviewers No assessment of quality was undertaken Meta-analysis conducted using the Mantel-Haenszel method (fixed effects) Results presented as pooled RR | High quality
Limited validity
- Included non-randomised studies |

Abbreviations: RD, risk difference; OP, organophosphorus; RCT, randomised controlled trial