Controversies in the management of organophosphate pesticide poisoning

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ABSTRACT

Acute poisoning with organophosphorous (OP) pesticides frequently causes ill-health and death all over the world. The treatment of OP poisoning is primarily aimed at reversing the effects of the compound by administration of atropine. A second class of compounds—oximes, capable of regenerating the active enzyme from the OP-cholinesterase complex, is also available to treat OP poisoning. Pralidoxime is the oxime most often used worldwide.

The low propensity to aging with diethyl organophosphorous poisoning may allow reactivation of the acetylcholinesterase after several days, when the poison concentration drops. The usefulness of oximes has however been challenged over the past 20 years by physicians in many parts of the world who have failed to see any benefit in their clinical practice. We have carried out a systematic search to find clinical trials, both randomized and nonrandomized involving the management of OP poisoning. The clinical benefits of oximes in OP poisoning is not clear, being limited by the type of OP, poison load, time to start therapy and dose of oximes. Hence, one is left with a doubt as to whether one could use oximes at all in OP poisoning? A high-quality randomized clinical trial on a large number of subjects comparing the current World Health Organization-recommended regimen with a placebo to assess the value of pralidoxime in acute OP poisoning, may answer the above question.

KEY WORDS: Clinical trials, organophosphate poisoning, pralidoxime

Background

Poisoning with organophosphorous pesticides (OPs) frequently causes ill-health and death, particularly in developing countries. The number of intoxications with OPs is estimated at some 3,000,000 per year.[1] Fatality rates of 20% are common and the World Health Organization (WHO) has estimated that 200,000 people die each year from pesticide poisoning.[2] although the accuracy of these figures is keenly debated.[3] Unfortunately, the widespread use of OP pesticides in the developing world’s agricultural communities will make the reduction of deaths by primary prevention a difficult task.

OPs act primarily by inhibiting acetylcholinesterase (AChE), thereby allowing acetylcholine to accumulate at cholinergic synapses, disturbing transmission at parasympathetic nerve endings, sympathetic ganglia, neuromuscular endplates and certain central nervous system (CNS) regions. Standard treatment includes attempts to reduce OP absorption with gastric lavage and/or activated charcoal, plus administration of atropine and oximes to counter the cholinergic effects of the pesticide.[4] Although the use of high doses of atropine is well established, the use of oximes is more controversial.

Oximes reactivate AChE by removing the phosphoryl group. Pralidoxime is the oxime most often used worldwide and occurs in two common forms: the chloride (2-PAM; molecular weight 173; used worldwide) and the mesylate.[5] The great majority of its effects are on the peripheral nervous system, since its lipid solubility is low and its entry into the CNS limited. Atropine works at muscarinic synapses, competitively antagonizing the accumulated acetylcholine. The main therapeutic effect of pralidoxime is predicted to be the recovery of neuromuscular transmission at nicotinic synapses. Although oximes should be given as soon as possible before aging takes place, a beneficial response as long as 24 hours after exposure has been reported.[6] Oximes are believed to be effective and to be especially useful in treating moderate or severe OP poisoning. Oximes may also reverse the CNS effects of OP.[7]

AChE aging is particularly rapid with dimethylphosphoryl compounds and may thwart effective reactivation by oximes, particularly in suicidal poisoning with excessive doses. In contrast, patients with diethyl OP poisoning may particularly benefit from oxime therapy, even if no improvement is seen.

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Received: 8.6.2006
Revised: 16.11.2006
Accepted: 4.12.2006

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Educational Forum

Indian J Pharmacol  April 2007  Vol 39  Issue 2  71-74
during the first days when the poison load is high. The low propensity to aging with diethyl OP poisoning may allow reactivation after several days, when the poison concentration drops.[11] Further, it has been reported[10] that the supplemental use of oxime cholinesterase reactivators (such as pralidoxime) reduces the incidence and severity of developmental defects in chick embryos exposed to known teratogens such as parathion, bidrin, carbachol and neostigmine. This protective effect of the oximes was shown to be dose-related.

Of late, clinical experience in the developing nations has led to doubt regarding the effectiveness of oximes in the management of OP poisoning. There are few randomized clinical trials (RCTs) conducted on this aspect with variable outcome. Hence, we carried out a systematic search for such RCTs to look for evidence of oximes producing clinical benefit in OP-poisoned patients.

Methods of Review

We carried out a systematic search for clinical trials by searching Pubmed, Ovid, Medline and Cochrane databases, cross-referencing from other articles. The web was also searched using [www.google.com] and the keywords “organophosphate, poisoning, overdosage, oxime and trial.”

Results

The initial standard database searches located four RCTs and two nonrandomized trials. We also found one paper and one meeting abstract that described two other small clinical trials. All identified studies assessed pralidoxime; clinical trials of obidoxime were done in one study only.

Randomized Clinical Trials

Trial 1

In this trial (conducted in the year 2005), 21 cases were recruited: 11 moderately severe and ten severe cases admitted to the Medical ICU of Christian Medical College, Vellore, India.[11] In the moderately severe group, six were allocated to the placebo arm and five to the treatment group. In the severe group, five belonged to the placebo group and five to the treatment group. While 12 g PAM infusion/day was used for severe cases for three days, only 4 g/day was used for moderate cases also for 3 days. Placebo group was given saline infusion. The authors concluded that treatment with PAM did not make any difference in OP poisoning. The more useful treatment options are anticholinergic drugs like atropine and supportive treatment with assisted ventilation.

Trial 2

In this study on the effect of oximes on nerve agents and pesticide poisoning, the authors found that respiratory complications were more common in the group treated with obidoxime or 2-PAM.[12] Details of the type of study are not available. Mortality was 9% (4/43) in the group treated with atropine, 50% (6/12) in the group treated with obidoxime and atropine and there was no mortality in the group treated with 2-PAM (eight patients).

Trial 3

Seventy-two patients were recruited for this study conducted between August 1991 and December 1992 at the Christian Medical College in Vellore, India.[13,14] 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 4 days without a loading dose (termed ‘high dose’). This RCT reported an increased mortality rate (22% vs 14%: odds ratio (OR) of 1.77, 95% confidence interval (CI) 0.52–6.0) and increased requirement for ventilation (67% vs 47%; OR 2.04, 95% CI 0.78–5.3) among patients who received the infusion as compared to those who received the bolus dose. 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’.

Trial 4

In this RCT, a total of 110 adult patients were recruited[15,16] and it compared ‘high-dose’ pralidoxime (i.e., 12 g by continuous infusion without loading dose) with the placebo saline infusion. The ‘high-dose’ regimen was associated with a significantly higher risk of death (29% vs 5%: OR 7.1, 95% CI 1.9–26.0) and increased requirement for ventilation (67% vs 40%; OR 3.1, 95% CI 1.4–6.7). The authors concluded that 2-PAM ‘has no role in the management of patients with organophosphorus poisoning and does more harm than good’.

Nonrandomized Clinical Trials

Trial 1

In this trial, 30 patients of moderate to severe OP poisoning were recruited and assigned to two groups.[17] This study was carried out in the department of Anaesthesiology, Pandit B. D. Sharma PGIMS Rotak, Haryana, India. One group (group I) received atropine alone and the other group (group II) received atropine and PAM. PAM neither improved the atropine profile in group II patients as compared to group I nor did it significantly change the ventilatory profile in the two groups. Mortality was negligible in both the groups. The authors concluded that their data did not support the widely accepted use of pralidoxime in the treatment of moderate to severe OP poisoning as it does not have any added advantage over atropine.

Trial 2

In another study in Sri Lanka, a total of 45 patients (21 in the study group and 24 in the control group) of moderate to severe OP poisoning were recruited.[18] In addition to general and supportive measures, atropine was given intravenously to all patients in amounts sufficient to maintain the pulse rate >120/minute and to keep the pupil fully dilated. Patients in the control group were also given a median of 4 g PAM intravenously during the first 24 h of treatment. Thereafter, PAM was given intravenously at a 1 g daily dose for up to five days. There were no significant differences between the study and control groups with regard to any of the outcomes such as median atropine requirement in first 24 hours, patient with intermediate syndrome and median hospital stay (days) or the patient needing intensive care treatment or ventilation.

Trial 3

A trial of pralidoxime was carried out in Tehran, Iran, during the early 1990s.[19] Out of 34 patients, 17 patients received atropine alone while 17 received 600-800 mg pralidoxime every 4-8 h for 4 days in addition to atropine. The pralidoxime dose was based on the patient’s condition.
All patients presented within ten hours of pesticide ingestion; 35% of control patients had ingested diethylphosphorylated OPs as compared to 29% of the pralidoxime plus atropine-treated patients. Pralidoxime use did not result in any significant reduction in the number of patients requiring ventilation (41% vs 47%; OR 0.79, 95% CI 0.20-3.0) or the number of patients dying (18% vs 18%; OR 1.0, 95% CI 0.17-5.8). The authors concluded that atropine alone should be used in the treatment of acute OP poisoning.

Trial 4

Another study has been published only in the form of an abstract.[20] Twenty OP-poisoned patients were included in this trial of two vials or four vials of pralidoxime iodide, but neither trial design nor results are apparent from the abstract. We have been unable to elicit any response from the author. It seems unlikely that conclusive evidence will result from such a small trial.

Discussion

The clinical benefits of oximes in OP poisoning is not clear, being limited by the type of OP, poison load, time to start therapy and dose of oximes.[1,2] In an evaluation using meta-analytic techniques, Peter et al.[22] observed that there was no statistically significant association of oxime therapy with mortality, ventilator requirements or the incidence of intermediate syndrome. Further, they reported that there was an increased need for intensive care therapy when oximes were used. They concluded that use of oximes in OP poisoning was associated with either a null effect or possible harm. This raises a basic question, i.e., does pralidoxime administration improve outcome? There are four published RCTs of pralidoxime in 266 patients with acute OP poisoning. These studies have since been used to argue that oximes should not be used in acute OP poisoning.[23] De Silva et al. compared atropine for the treatment of OP poisoning vs atropine and pralidoxime in a controlled trial. No benefit from pralidoxime was found, however, the dose of pralidoxime given was small.[10] Johnson and Vale have argued that failure of oxime therapy does not indicate ineffectiveness of the drug nor does it necessarily indicate delay in administration; indeed, failure of treatment is usually a function of inadequate dosing.[24] Considering the available data, it seems that about 500 mg/h should be infused to maintain adequate therapeutic concentrations of pralidoxime (about 4 mg/L) in a severely poisoned adult. Johnson and Vale emphasize that dosage should be maintained continuously until clear, irreversible, clinical improvement is achieved. This may take many days as the residual poison has to be cleared from the body.

A prospective study in Iran by Balai-Mood and Shariat compared atropine, obidoxime + atropine and pralidoxime + atropine for OP pesticide poisoning. Although not statistically significant, AChE reactivation was only observed in the pralidoxime group. There were no deaths in the pralidoxime group and doses of pralidoxime used were well tolerated. (8 mg/kg followed by 2 mg/kg/h). A high rate of hepatotoxicity was observed in the obidoxime group.[12]

In one study using pralidoxime methylsulphate, it was found that following parathion poisoning, enzyme reactivation could be achieved in some patients at oxime concentrations as low as 2.88 mg/L. However, oxime concentrations as high as 14.6 mg/L did not produce any effect in others. These authors concluded that the therapeutic effect of oximes seemed to depend on the plasma concentration of the OP agent with the benefits being minimal at high blood levels of OP.[25]

Current WHO guidelines recommend giving a 30 mg/kg loading dose of pralidoxime over 10-20 minutes followed by a continuous infusion of 8-10 mg/kg/h until clinical recovery or seven days have elapsed, whichever is later.[1,3] But the studies reported did not evaluate the current WHO-sponsored recommendations. This is one of the major drawbacks of these studies.

It is likely that the ‘high-dose’ regimen of pralidoxime used in Vellore did not produce an effective plasma concentration, a loading dose of pralidoxime being required to reach an effective plasma concentration. This may be the reason for the observed mortality and lack of efficacy of the higher dose infusion (without the loading dose). An alternative interpretation of the lower mortality and lower need for ventilation in patients receiving the lower bolus dose of pralidoxime would therefore be that although a bolus dose when given alone, produces an effective concentration for a limited period of time, does achieve higher plasma concentrations.

However, the worse outcome seen in patients who received pralidoxime infusion suggests that it harms patients. However, sicker patients might also have been randomized to this treatment arm and that may be the reason for the failure of the oxime therapy.

The reports of the two small studies from Iran and north India provide too few details of trial design for any conclusions to be safely drawn.

Conclusion

In view of the reported randomized and nonrandomized trials, one may wonder whether one could use oximes at all in the management of OP poisoning. Inspite of certain flaws in the methodology, it is quite possible that their conclusions are correct.

There is however, a pressing need for a large high-quality RCT comparing the current WHO-recommended regimen with a placebo to assess the value of pralidoxime in acute OP poisoning. Such a trial may well confirm the earlier findings but would help establish the potential role of oximes in OP poisoning more firmly.

References