Continuous pralidoxime infusion versus repeated bolus injection to treat organophosphorus pesticide poisoning: a randomised controlled trial

Kirti S Pawar, Ramesh R Bhoite, Chandrakant P Pillay, Sujata C Chavan, Dhananjay S Malshikare, Saraswati G Garad

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Giriraj Hospital and Intensive Care Unit, Baramati, Pune, Maharashtra, India (K S Pawar MBBS, R R Bhoite MD, C P Pillay BHMS, S C Chavan BHMS, D S Malshikare BHMS); **and Department of Preventive & Social Medicine, B J Medical College, Pune, Maharashtra, India** (S G Garad MSc)

Correspondence to:
Dr Kirti S Pawar
Giriraj Hospital and Intensive Care Unit, Indapur Road, Baramati, Pune District, Maharashtra 413 102, India
kirtispawar@yahoo.co.in

Summary

Background **The role of oximes for the treatment of organophosphorus pesticide poisoning has not been conclusively established. We aimed to assess the effectiveness of a constant pralidoxime infusion compared with repeated bolus doses to treat patients with moderately severe poisoning from organophosphorus pesticides.**

Methods **200 patients were recruited to our single-centre, open randomised controlled trial after moderately severe poisoning by anticholinesterase pesticide. All were given a 2 g loading dose of pralidoxime over 30 min. Patients were then randomly assigned to control and study groups. Controls were given a bolus dose of 1 g pralidoxime over 1 h every 4 h for 48 h. The study group had a constant infusion of 1 g over an hour every hour for 48 h. Thereafter, all patients were given 1 g every 4 h until they could be weaned from ventilators. Analysis was by intention to treat. Primary outcome measures were median atropine dose needed within 24 h, proportion of patients who needed intubation, and number of days on ventilation. The study is registered at http://www.clinicaltrials.gov with the identifier NCT00333944.**

Findings **100 patients were assigned the high-dose regimen, and 100 the control regimen. There were no drop-outs. Patients receiving the high-dose pralidoxime regimen required less atropine during the first 24 h than controls (median 6 mg *vs* 30 mg; difference 24 mg [95% CI 24–26, p<0·0001]). 88 (88%) and 64 (64%) of controls and high-dose patients, respectively, needed intubation during admission to hospital (relative risk=0·72, 0·62–0·86, p=0·0001). Control patients required ventilatory support for longer (median 10 days *vs* 5 days; difference 5 days [5–6, p<0·0001]).**

Interpretation **A high-dose regimen of pralidoxime, consisting of a constant infusion of 1 g/h for 48 h after a 2 g loading dose, reduces morbidity and mortality in moderately severe cases of acute organophosphorus-pesticide poisoning.**

Introduction

Self-poisoning is a major cause of death in developing countries. Intentional ingestion of organophosphorus pesticides has been common for the past 40 years and is now the most important form of poisoning in poorer people across central and southern parts of India.[1] The standard treatment for poisoning with organophosphorus pesticide is to give intravenous atropine and oximes.[2] Treatment with atropine, which inhibits the effects of acetylcholine at muscarinic receptors, is well established. Reactivation of inhibited acetylcholinesterase by treatment with oximes, such as pralidoxime, might also confer benefits. However, neither the effectiveness of oximes nor the optimum dose schedule for such treatments has been established.[3–7]

A dose of 1 g oximes every 4–6 h has been the standard regimen in Asian district hospitals, but many clinicians remain unconvinced by its effectiveness.[4] Since organophosphorus pesticides kill hundreds of thousands of people in rural Asia every year, it is essential to establish an effective regimen for treatment of such cases of poisoning. Randomised controlled trials during the 1990s compared a 12 g infusion of pralidoxime over 3–4 days with a 1 g bolus dose and with placebo.[8,9] The investigators reported no benefit from pralidoxime, and increased mortality in those receiving the infusion.[8,9] They concluded that pralidoxime should not be given to organophosphorus-poisoned patients.[3]

However, the dose regimen used in these trials might not have been ideal, since therapeutic concentrations were obtained only rarely during the treatment.[4,5] Treatment with oximes might have been rendered ineffective because either the dose or the duration of therapy was not sufficient. Further, many patients in the trials presented late and had taken dimethyl pesticides.[8,9] If treatment with oximes is delayed, the phosphate bound to the inhibited acetylcholinesterase loses an alkyl group and becomes resistant to pralidoxime therapy.[7] The loss of an alkyl group occurs more quickly for dimethyl organophosphorus pesticides such as dimethoate than for diethyl organophosphorus pesticides such as chlorpyrifos.[7,10] Thus, treatment for poisoning with dimethyl pesticides must be started much earlier than for other diethyl pesticides, and late treatment could bias results.

On the basis of tests in vitro and in animals, the minimum concentration of pralidoxime in plasma at which this treatment is effective was thought to be 4 mg/L.[11] Evidence suggests, however, that the concentration of pralidoxime in the blood might need to be higher than this to antagonise the toxic effects of many

pesticides.[7] Thus a bolus-loading infusion followed by a maintenance infusion might be the best regimen.[7] On this basis, the World Health Organization has proposed that patients be given about 30 mg/kg pralidoxime salt as a loading dose, followed by an infusion of at least 8 mg/kg per h (in a 50 kg south Asian patient this is roughly equivalent to 1–2 g bolus followed by 0·5 g/h).[7,12,13] However, no trials have yet been done to find out whether such a regimen can reduce morbidity and mortality in severely poisoned patients.[4] Although two small uncontrolled case series suggested that pralidoxime could have possible benefit if given according to the WHO regimen,[4] a systematic review reported that there was insufficient evidence to establish the effectiveness of oximes in acute organophosphorus pesticide poisoning.[4,14]

Our hospital has typically used a regimen of 1 g every 4 h in organophosphorus-poisoned patients, but we were unconvinced about the effectiveness of this regimen, since many patients required ventilation for more than 10 days. We informally treated several patients with the WHO-recommended regimen but noted little improvement in morbidity or mortality. Since pralidoxime has a high therapeutic index, we then decided to do a randomised controlled trial with higher doses—ie, to compare a 1 g infusion every h (24 g/day) with the standard regimen of 1 g every 4 h (6 g/day), after a 2 g loading dose. Our aim was to assess the effectiveness of a constant high-dose pralidoxime infusion, compared with repeated bolus doses, in patients poisoned with organophosphorus pesticides.

Patients and methods

Study participants

The study was a single-centre, open randomised controlled trial done at a 50-bed private hospital in Pune District, Maharashtra, India. The hospital has an 18-bed intensive care unit and is the best-equipped hospital for a population of 500 000 who live within 100 km. Direct admissions and transfers are accepted from nearby government and private hospitals. Patients pay for the cost of their treatment, although reductions are offered on the basis of ability to pay.

We aimed to recruit all patients with a history of poisoning by an organophosphorus pesticide between May 28, 2000, and June 26, 2003, and with clinical features of poisoning. Exclusion criteria were age younger than 12 years, presence of chronic disease or malignancy, pregnancy, presentation later than 24 h after ingestion, and failure to resuscitate successfully in the 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. Serum butyrylcholinesterase activity was measured on admission for all patients but results were not available in time to guide recruitment. The ethics committee of the participating hospital approved the protocol of this trial. Relatives of recruited patients provided written informed consent for participation.

Methods

All patients with acute organophosphorus-pesticide poisoning were assessed and resuscitated in the emergency room before admission to the intensive care unit. This unit has a ratio of one nurse, one doctor, and one ventilator to every two patients. After admission, patients were treated simultaneously with oxygen and intravenous atropine, pralidoxime, and fluids. Staff did nasogastric lavage, removed contaminated clothes, and washed patients. All patients were provided with oxygen by mask. Criteria for intubation were failure to maintain arterial oxygen saturation above 90% with 60% F_1O_2 or failure to maintain a respiratory rate above 10 per min.

Every patient was given 1·8–3·0 mg atropine on admission. We then started an infusion of atropine by syringe pump, with intermittent boluses to achieve control of secretions from the tracheobronchial tree, return pupils to their normal size, and stabilise the pulse rate at between 80 and 100 bpm. Rather than attempt to achieve a definite tachycardia, we aimed to reverse bradycardia.

During resuscitation, a blood sample was obtained for measurement of serum butyrylcholinesterase. The initial loading dose of 2 g pralidoxime was then given over 30 min by syringe pump. The first dose of pralidoxime was obtained from intensive care unit stocks; subsequent doses were bought by the patients' relatives from a local pharmacy. The pralidoxime salt used was pralidoxime iodide (Trisachem Pharmaceuticals, India).

After aspirating patients' stomach contents through a nasogastric tube, we did gastric lavage with 250 mL volumes of dilute potassium permanganate until the returning fluid was clear (generally 2–4 L). Some patients were intubated before lavage; this decision was made on the basis of the patient's clinical status. At the end of gastric lavage, crushed tablets of activated charcoal were left in the stomach and replaced 8 hourly for the next 48 h. Clinicians applied supportive measures, such as central venous catheterisation, intravenous fluids, urinary catheterisation, antibiotics (cefotaxime, metronidazole, gentamicin, or a combination of these), and ranitidine as and when needed. Patients were monitored continuously by non-invasive means to measure their blood pressure, heart rate, respiratory rate, and arterial oxygen saturation.

After initial resuscitation, and within 1 h of admission, study personnel met relatives of eligible patients, and asked them to give written informed consent for enrolment in the trial. The identity of the organophosphorus pesticide ingested was determined on the basis of the observations of relatives, evidence from empty bottles of pesticides, and the clinical signs and symptoms. Enrolled patients were then randomly assigned by use of a block randomisation schedule, which

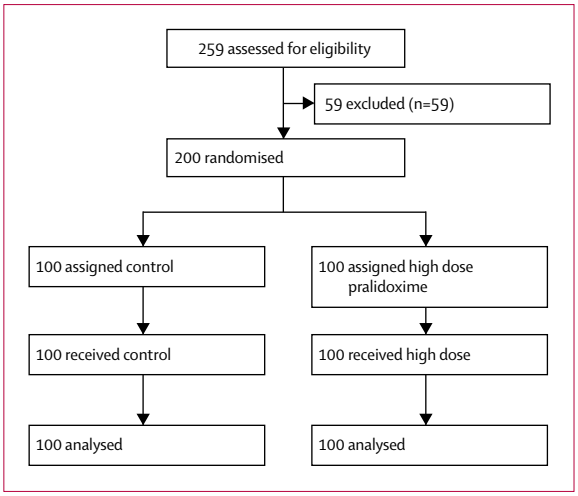

Figure: **Trial profile**

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.

After the loading dose of pralidoxime, every patient was given an infusion of 1 g over 1 h either every 4 h (control group) or every hour (study group) for 48 h. Thereafter, both groups received 1 g every 4 h until patients were weaned off ventilators. 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.

Unintubated patients and successfully weaned extubated patients were monitored for signs of intermediate syndrome. These include ocular, bulbar, proximal limb, or neck flexion weakness; tachypnoea; sweating; use of accessory muscles of respiration; and respiratory muscle weakness. After about 4 or 5 days, physicians considered the need for tracheostomies in intubated patients who were expected to continue to need ventilatory support. Patients were kept in intensive care for a minimum of 2 days if they did not need intubation, or for 2 days after satisfactory weaning from a ventilator.

We set primary outcomes as median atropine dose needed within 24 h of admission, proportion of patients who required intubation, and number of days on ventilation. Secondary outcomes were pneumonia (aspiration or ventilator-associated), mean systolic and diastolic blood pressure in first 24 h, and death. 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. Fibreoptic bronchoscopy was done as indicated. Patients were monitored daily by the study doctors for adverse events such as dizziness, raised blood pressure, blurred vision, and acute cardiorespiratory problems. Serum butyrylcholinesterase was assayed by the method of Ellman and co-workers[15] with the cholinesterase kit produced by Raichem (San Diego, CA, USA).

	Control group (n=100)	Study group (n=100)
Men	52	57
Oral route of consumption	94	98
Ingestion of diethyl pesticides*	41	23
Ingestion of dimethyl pesticides†	59	77
Intubated during resuscitation	69	63
Median (IQR) age (years)	29 (22–35)	28 (22–33)
Median (IQR) time between ingestion and admission (min)	112·5 (60·0–150·0)	120·0 (90·0–142·5)
Median (IQR) quantity of poison consumed (mL)	15 (10–20)	15 (15–20)
Median (IQR) Glasgow coma score	10 (8–12)	10 (10–12)
Median (IQR) serum butyrylcholinesterase activity (IU/L)‡	808·0(534·8–911·0)§	866·0 (751·8–939·0)¶
Mean (SD) pulse (bpm)	50·5 (7·85)	50·8 (9·35)
Mean (SD) systolic blood pressure (mm Hg)	110·2 (14·72)	116·2 (14·79)
Mean (SD) diastolic blood pressure (mm Hg)	70·3 (10·78)	74·5 (10·77)

Data are count (percentage) for categorical variables; mean (standard deviation) for normally distributed continuous variables, median (interquartile range—25th to 75th percentile) for other continuous variables. *Chlorpyrifos (40 control, 22 study), quinalphos (1, 1). †Dimethoate (45, 65), monocrotophos (5, 6), methyl parathion (6, 5), malathion (2, 2), fenitrothion (1 control). ‡Normal range: 2710–11 510 IU/L. §n=93. ¶n=83.

Table 1: **Baseline demographic and clinical characteristics at admission**

Statistical analysis

On the basis of the size of our study population and the results of a pilot study, we estimated that our trial had about 90% power to detect, at the 5% significance level, a 20% difference in proportion of patients who required intubation (90% intervention group *vs* 70% control group). The minimum sample size calculated for each group was 84; expecting some dropouts, we chose a sample size of 100 for each group. Since pralidoxime has a high therapeutic index, we did not expect adverse effects related to higher doses, and an interim analysis was not planned.

We managed data with SPSS (release 11·5, Chicago, IL, USA) and Stata (version 9, College Station, TX, USA). Analysis was based on intention to treat—ie, data from all eligible patients were analysed in the groups to which they were allocated. Continuous variables were investigated for departure from normality by use of the Shapiro-Wilk test. For the normally distributed outcomes, we calculated the mean difference and did *t* tests to compare the treatment groups. Linear regression was used to estimate the treatment effect, adjusting for baseline measurement (analysis of covariance [ANCOVA]). For the skewed continuous outcomes, we did non-parametric Mann-

Whitney tests to investigate differences between the treatment groups. To estimate the treatment effect, we calculated the difference in medians. For binary outcomes, the treatment groups were compared by use of Fisher's exact test. To adjust for various factors, we did multivariate logistic regression (with outcome as the dependent variable, and study arm and type of poisoning as covariates). The resulting odds ratios were then converted to risk ratios with the formula: risk ratio=odds ratio/(1–outcome incidence in control group+outcome incidence in control group×odds ratio).[16]

We also did a post-hoc subgroup analysis to establish whether treatment effects were consistent between dimethyl and diethyl pesticides. We analysed the data with a further adjusted ANCOVA and logistic regression (for outcomes for which sufficient events occurred) to control for class of pesticide.

The Lancet requested an independent site visit, during which a reviewer checked our medical notes against the database for 25% of the patients, chosen at random. The study is registered at the US National Institutes of Health website http://clinicaltrials.gov as "Study to know the efficacy of high doses of pralidoxime in patients of organophosphorus poisoning" with the protocol identification number of NCT00333944.

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

During the study period, 259 patients with organophosphorus pesticide poisoning were admitted to Giriraj Hospital and intensive care unit, of whom 200 were recruited into the randomised controlled trial (figure). 59 patients were excluded: 56 were asymptomatic (two after receiving pralidoxime at a primary hospital), two presented more than 24 h after exposure, and one had cancer. None of the 259 eligible patients refused to participate. The 200 enrolled patients were randomly assigned into two groups of 100 patients each. No patients withdrew from the study, and all 200 patients were followed up.

Table 1 shows baseline demographic and characteristics of clinical presentation for the two treatment groups. Small but significant differences were noted for the class of organophosphorus pesticides ingested, blood pressure, Glasgow coma score, and serum butyrylcholinesterase activity on admission. More patients in the study group than in the control group had ingested dimethyl pesticides (which are thought to respond less well to oximes than diethyl pesticides[10]). The estimated quantities of poison consumed varied from 5 mL to around 50 mL. All patients recruited to the trial had serum butyrylcholinesterase activity below 50% of the lower range of normal in our laboratory (1400 U/L). All asymptomatic patients who were excluded from the study had values greater than 1400 U/L.

Table 2 shows that the higher dose of pralidoxime was of more benefit to patients than the low-dose infusion given to controls. The amount of intravenous atropine given within 24 h was higher for controls than for study patients. Numbers with neck-muscle weakness and need for ventilatory support were significantly higher in the control group than in the high-dose pralidoxime group. Controls also required ventilator support for significantly longer than study patients. Compared with those in the control group, there were fewer deaths (1% *vs* 8%) and far fewer cases of pneumonia (8% *vs* 35%) in patients given a high-dose regimen of pralidoxime.

	Control group (n=100)	Study group (n=100)	Difference or relative risk(95%CI)	p
Primary outcomes				
Median days ventilated	10 (8–12)*	5 (4 to 5)†	5 (5–6)	<0·0001
Median atropine dose in first 24 h (mg)	30 (25 to 45)	6 (4 to 6)	24 (24–26)	<0·0001
Neck muscle weakness	94 (94%)	80 (80%)	0·85 (0·76–0·95)‡	0·0054‡
			0·86 (0·65–0·98)§	0·0054§
Intubated during admission	88 (88%)	64 (64%)	0·72 (0·62–0·86)	0·0001
Intubated after randomisation	19/31 (61·3%)	1/37 (2·7%)	0·044 (0·063–0·31)‡	<0·0001‡
			0·045 (0·005–0·31)§	0·0001§
Secondary outcomes				
Deaths	8 (8%)	1 (1%)	0·13 (0·016–0·98)‡	0·0349‡
			0·11 (0·01– 0·84)§	0·00350§
Pneumonia	35 (35%)	8 (8%)	0·23 (0·11–0·47)‡	<0·0001‡
			0·23 (0·10–0·47)§	<0·0001§
Mean systolic blood pressure in first 24 h (mm Hg)	115·4 (6·10)¶	136·2 (4·97)‖	20·6 (19·0–22·2)	<0·0001
Mean diastolic blood pressure in first 24 h (mm Hg)	75·6 (4·96)¶	84·1 (2·56)‖	8·3 (7·2–9·5)	<0·0001

*n=80. †n=63. ‡Unadjusted values. §Adjusted values. ¶n=97. ‖n=99.

Table 2: **Summary of primary and secondary outcomes with comparative statistics**

No substantial adverse effects (such as nausea, vomiting, or diastolic hypertension) were noted in trial patients. However, both diastolic and systolic blood pressure were higher over the first 24 h in study patients than in controls. All patients were followed-up for 52 weeks after discharge; no delayed adverse effects or neurological complications were noted in either group.

Adjustments to control for class of pesticide, using ANCOVA and logistic regression (for outcomes for which sufficient events occurred) made little difference to the estimates. The odds ratio after adjustment was 0·27 (95% CI 0·1–0·73) for neck muscle weakness; 0·018 (0·0021–0·15) for intubation post-randomisation; 0·10 (0·012–0·83) for death; and 0·16 (0·069–0·37) for pneumonia.

Discussion

We report that higher doses of pralidoxime than the standard regimen reduced the need for atropine within 24 h of admission and the severity of respiratory failure, as measured by need for intubation and days on ventilation. Secondary outcomes, such as the occurrence of pneumonia and the number of deaths, were also reduced by our study regimen of high-dose pralidoxime. Although some studies have suggested that dimethyl and diethyl pesticides differ in their response to oximes,[10] we identified no apparent difference in response to treatment for poisoning with the two classes of pesticide.

The pronounced link between a high-dose pralidoxime regimen and prevention of aspiration pneumonia was not expected, since most aspiration would have occurred before hospital admission and thus before treatment. We think that this effect probably occurred because patients given high doses needed ventilation for a shorter time than those on the control regimen. Because controls mobilised substantially later, these patients had more pulmonary complications caused by both prehospital aspiration and ventilation than did patients given high doses of pralidoxime.

We expected pralidoxime treatment to be associated with adverse effects such as dizziness, diastolic hypertension, vomiting, and blurred vision. However, our results show only mild increases in diastolic and systolic blood pressure. These side-effects might result from treatment with pralidoxime at rates faster than 200 mg/min,[17–19] compared with the much slower rates used in our study regimen.

This study had several limitations. First, the design was not a double-blind randomised controlled trial. However, blinding bias was kept to a minimum since several outcomes could be objectively measured—in particular death and intubation. Pneumonia was also diagnosed by a physician who was unaware of the allocation status of the patient. Second, as the facility for measurement of organophosphorus pesticide in blood was not available in our institute, we were unable to confirm the suspected identity ingested poison or measure the concentration of pralidoxime in plasma. We did serum butyrylcholinesterase measurements, which are not good indicators of clinical severity, but were unable to measure more specific indicators such as cholinesterase concentrations in red blood cells. Third, the study was biased towards moderately ill patients because institutional policy did not allow us to enrol severely intoxicated patients. The effects of pralidoxime in cases of severe poisoning will need to be assessed. Fourth, the randomisation method seemed to produce differing groups at baseline. For example, ingestion of dimethoate (oral dose producing 50% lethality in rats=250 mg/kg) was more common in the study group, whereas ingestion of chlorpyrifos (135 mg/kg) was more common in controls. Although indices of toxic effects for animals are not good markers of effects in humans,[10] this gave us cause for concern. However, statistical tests clarified that these baseline imbalances had no significant effects on outcome. Finally, some of the outcomes initially included in our protocol were not independent—eg, neck and respiratory weakness are both associated with the so-called intermediate syndrome, and length of time in intensive care was dependent on the duration of intubation. We therefore, post hoc, removed these dependent outcome variables (intermediate syndrome and days in intensive care).

In conclusion, although a small study, we report pronounced benefits from a high dose infusion of pralidoxime—2 g of pralidoxime as a loading dose, followed by 1 g over an hour every hour for 48 h in patients with moderately severe poisoning. We will need to compare this high-dose regimen with the much lower-dose regimen recommended by WHO. Our findings contrast with those of Cherian and co-workers,[8,9] who used a low-dose bolus pralidoxime regimen. We suggest that patients should not be given pralidoxime by repeated boluses. Unfortunately, pralidoxime is expensive—our high-dose regimen costs around US$400 for the first 48 h, which is far beyond the capacity of most patients in rural Asia. More affordable sources of pralidoxime will be needed to relieve the heavy burden of organophosphorus poisoning on both rural Asian communities and their health care systems.

Contributors

K S Pawar contributed to conception and design of the study, wrote the protocol, analysed results, and wrote and edited the report. R R Bhoite, C P Pillay, and S C Chavan gathered and extracted data. D S Malshikare generated the randomisation sequence and allocation programme. S G Garad did the statistical analysis of this trial and generated results. All authors have seen and approved the final version.

Conflict of interest statement

We declare that we have no conflict of interest.

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