ORIGINAL ARTICLE

A Study on Two Dose Regimens of Pralidoxime in the Management of Organophosphate Poisoning

MAHADEVAIAH MAHESH*, MOHAN GOWDAR, CHILKUNDA RAVIPRAKASH VENKATESH

Department of General Medicine, JSS Medical College and Hospital, JSS University Mysore, India

Abstract

Background: The role and proper dose of pralidoxime in the treatment of Organophosphorus (OP) compounds poisoning is an unresolved issue .This study was designed to compare the regimen recommended by the World Health Organization (WHO) with the commonly used standard regimen of pralidoxime.
Methods: This was a randomized open labeled prospective study on OP poisoned patients admitted to JSS Hospital, Mysore, India during November 2009 to January 2012. WHO regimen of 2 g pralidoxime bolus followed by 8mg/kg/h infusion (study group) compared with standard regimen of 2 g pralidoxime bolus followed by 1g 6 hourly (control group).
Results: In total, 82 patients were studied. Thirty-seven patients were randomized into the study group and 45 patients to the control group. All patients had moderate clinical severity. Although fewer patients in the study group required mechanical ventilation in comparison to the controls (12 vs. 22), the difference was not significant (P = 0.13). The death rate was lower in the study group though the difference was not also significant (P = 0.17). Mean (SD) duration of mechanical ventilation in the study group was significantly lower than controls (4.1 (1.6) vs. 6.6 (1.7) days; P = 0.01). Mean dosage of atropine administered was significantly lower in the study group compared to controls (345.0 (90.6) vs. 933.1 (162.3) mg; P = 0.001). Furthermore, 15 controls (33.3%) developed intermediate syndrome whereas no patient (0%) in the study group had such complication, which showed a significant difference (P < 0.001).
Conclusion: A dose regimen of pralidoxime consisting of 2 g pralidoxime bolus followed by 8mg/kg/h infusion reduces morbidity and mortality in moderate cases of OP poisoning. The WHO dose regimen had significantly better outcomes compared to the standard dose regimen.

Keywords: Cholinesterase Reactivators; Clinical Trial, Organophosphate Poisoning; Oximes; Pralidoxime Compounds

How to cite this article: Mahesh M, Gowdar M, Venkatesh CR. A Study on Two Dose Regimens of Pralidoxime in the Management of Organophosphate Poisoning. Asia Pac J Med Toxicol 2013;2:121-5.

INTRODUCTION

Organophosphorus (OP) compounds are widely used as insecticides and pesticides (1). In many developing countries including India, OP compounds are easily available and are common cause of both intentional and accidental poisonings (2-5). OP insecticides were responsible for 50% of all poisoning-related deaths in India in the past 25 years, accounted for 75% of all poisonings (1). The annual incidence of OP poisoning worldwide is about 3 million with 220,000 deaths (2,3). It is estimated that OP pesticide self-poisoning causes approximately 200,000 deaths annually worldwide, mostly in the Asia-Pacific region and the mortality rate varies from 10 to 20% (4).

In most developing countries, we are facing with shortage of trained personnel for poisoning care, and also diagnostic and treatment facilities (5). Self-poisoning with OP compounds is a serious health problem especially in agricultural areas of developing countries (2). Being predominantly an agricultural country, OP compounds are used abundantly for farming in India. Hence, access to these hazardous chemical substances is easy (5). OP pesticides inhibit carboxylic esterase enzymes including acetyl cholinesterase (AChE) and plasma cholinesterase (PChE) through binding to the esteratic site on the AChE molecule, phosphorylating the enzyme. Binding to the esteratic site on the enzyme is stable and depending on the compound involved, it can last for hours or weeks (1). A phenomenon of enzyme aging occurs which involves cleavage of a free radical from the inhibited enzyme, making it resistant to reactivation. Restoration of AChE levels occurs by spontaneous or induced reactivation of the enzyme and also by new enzyme synthesis (5).

Two important agents used in the treatment of OP poisoned patients are atropine and pralidoxime. Atropine antagonizes the muscarinic effects of OP compounds. It is an established antidote and its use is indicated in OP poisoning. The other agent that has been used for four decades is pralidoxime, which acts by reactivating phosphorylated cholinesterase (1). It has been used as a complementary to atropine to treat features associated with stimulation of nicotinic receptors (7,8). Despite it has been used for decades, there is still controversy over the usefulness and dosage of pralidoxime (9-12). Reports of outstanding effectiveness of pralidoxime have been countered by studies showing disappointing results.

*Correspondence to: Mahadevaiah Mahesh, MD. Associate Professor, Department of General Medicine, JSS Hospital, Mahathma Gandhi Road, Mysore 570004, Karnataka State, India
Tel: +91 984 511 4166, E-mail: doctmahesh@yahoo.com
Received 27 March 2013; Accepted 23 September 2013

Currently, there is a wide disparity in the dosage of pralidoxime administered. Many centers do not use pralidoxime at all. The low dose regimen of 1g/day to 4-6g/day is the most widely used (and is also called standard regimen) (10). The dose regimen recommended by the World Health Organization (WHO) includes 30 mg/kg bolus followed by 8 mg/kg/h infusion (9). In addition, a very high dose regimen of pralidoxime (1g/h infusion) has also been recommended in a randomized controlled trial conducted in India (13). Nevertheless, the WHO regimen has not really been evaluated in direct comparison with the standard regimen in clinical studies. This study was therefore, conducted to compare the efficacy of the WHO regimen and the commonly used standard regimen.

METHODS

This was a randomized open labeled prospective study conducted at JSS Hospital, a tertiary care teaching hospital affiliated to JSS Medical College, JSS University. The study was done during a period of 51 months (November 2009 to January 2012). Patients presenting with history of OP poisoning were enrolled. The severity of poisoning in each patient was assessed with Peradeniya Organophosphorus Poisoning (POP) Scale (14). Exclusion criteria were (a) very severe poisoning (intubation required on admission or within two hours post-admission or POP score more than 7 at presentation) (b) poisoning with multiple toxic agents, (c) concurrent consumption of OP compounds with alcohol, (d) severe co-morbid conditions (chronic obstructive pulmonary disease, chronic kidney disease, ischemic heart disease, diabetes mellitus, severe anemia, asthma).

Ethical clearance was obtained from the JSS Medical College Institutional Ethical Committee (ethical code: JSS/MC/IEC/3086/2009-2010). Informed written consents were obtained from all patients or their legal entourage.

Patients were randomized to one of the two groups for pralidoxime therapy (Figure 1):

(a) Study group (WHO regimen); that received 2 g intravenous bolus pralidoxime followed by continuous infusion at 8 mg/kg/h for 5 days

(b) Control group (standard regimen); 2 g intravenous bolus pralidoxime followed by 1g/6 hourly bolus for 5 days.

The medication used was pralidoxime iodide manufactured by SK Pharmaceuticals, Hyderabad, India. All patients received 5 mg intravenous bolus atropine at presentation followed by 2-5 mg every 5-10 minutes until atropinisation, and subsequently continuous infusion to achieve control of secretions from trachea-bronchial tree and to maintain the heart rate at 80-100 beats/min.

Blood sample for measurement of PChE was taken at presentation and prior to initiation of treatment. PChE rather than AChE was measured due to lack of laboratory facilities in our center. PChE was measured by enzymatic method using butyrate and thiocholine as substrate (5).

The primary outcome parameter assessed was need for intubation. Secondary outcome parameters assessed were: (a) atropine requirement, (b) duration of ventilation, (c) development of intermediate syndrome, and (d) death.

Data were analyzed using SPSS version 16.0 for Windows (SPSS Inc., Chicago, IL). Analysis included descriptive statistics, contingency coefficient analysis with independent samples t-test and Mann-Whitney U test for non-normal data.

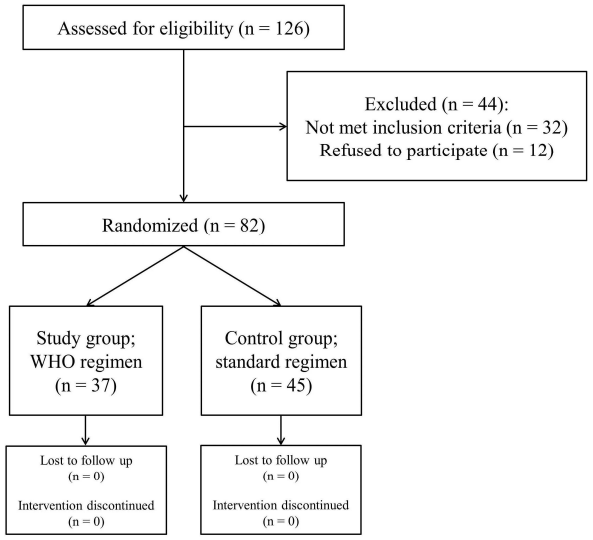

Figure 1. CONSORT diagram showing patient recruitments and exclusions in each arm of the study.

RESULTS

Demographic and clinical severity

Of the 126 patients enrolled, 32 patients were excluded and 12 patients refused to participate in the study. Of the remaining 82; thirty-seven patients were randomized into study group and 45 patients into control group. In total, 56 patients were men and 26 were women. There were more men than women in both groups (Table 1). The majority of subjects (42.7%) aged between 26 and 35 years. Regarding age and gender, there were no significant differences between two groups. All patients in both groups had moderate clinical severity (POP score between 4 and 7).

Treatment and outcomes

Mean time interval between poisoning and the onset of pralidoxime administration in the study group was 5.1 hours and in the control group was 5.3 hours which was not significantly different between the groups.

The median (IQR) of PChE in the study group was 1878 (4211) and in the control group was 2776 (3876.5) which was not significantly different between the groups. Thirty-four patients (41.5%) required mechanical ventilation. Of these, fewer patients belonged to study group though the difference was not significant (Table 1). Mean time interval between poisoning and intubation in study group was 6.1 (1.6) hours and in controls was 6.7 (1.5) hours which was not significantly different between the groups. Nevertheless, mean duration of mechanical ventilation in the study group

Table 1. Comparison of demographic features, treatments administered and outcome of study and control groups

Parameter (unit), report	Study group (n = 37)	Control group (n = 45)	P value
Age (years), mean (SD)	31.3 (8.9)	30.1 (7.3)	0.48
Male/Female, n	21/16	35/10	0.07
PChE (U/L), median (IQR)	1878 (4211)	2776 (3876.5)	0.30
Patients required mechanical ventilation, n (%)	12 (32.4)	22 (48.8)	0.13
Duration of mechanical ventilation (days), mean (SD)	4.1 (1.6)	6.6 (1.7)	0.01
Atropine (mg), mean (SD)	345.0 (90.6)	933.1 (162.3)	0.001
Intermediate syndrome, n (%)	0 (0)	15 (33.3)	< 0.001
Death, n (%)	4 (10.8)	10 (22.2)	0.17

was significantly lower than controls (4.1 (1.6) vs. 6.6 (1.7) days; P = 0.01). In addition, mean dosage of atropine administered was significantly lower in the study group compared to the controls (345.0 (90.6) vs. 933.1 (162.3) mg; P = 0.001). Furthermore, 15 controls (33.3%) developed intermediate syndrome whereas no patient (0%) in the study group had such complication, which shows a significant difference (P < 0.001). Although the number of deaths was lower in study group, this does not show any significant difference (P = 0.172). No adverse events directly attributable to pralidoxime were noted.

DISCUSSION

To the best of our knowledge, the present study is the second one which exclusively compared the efficacy of WHO recommended dose regimen of pralidoxime with the standard regimen. Results of our study revealed that there was no significant difference between the two groups with respect to the outcome measures of need for ventilation and mortality. However, significant differences in other outcome parameters, such as duration of ventilation, total dose of atropine requirement and development of intermediate syndrome were found which indicates that the WHO regimen is superior.

The only other study with a similar comparison was performed by Varghese et al., in which they found no statistically significant difference between the two regimens (15). In their study, patients who were partially treated with pralidoxime before arrival to their center were also included. This may affect their final results. The present study took up intact previously untreated cases only, and partially treated patients were excluded from the study. Moreover, the baseline characteristics of the two groups in the present study were similar.

There has always been controversy regarding the usefulness of pralidoxime in treatment of OP poisoned patients. It began when de Silva et al. found no benefit in a retrospective placebo controlled analysis (16). However, their study sample was small with only 43 patients who were treated with a low dose pralidoxime (4g bolus followed by 1 g/day). Subsequently, Johnson et al. compared 1g single bolus dose of pralidoxime with 12 g infusion over 4 days and found increased mortality rate and ventilation requirement in the infusion group (17). Cherian et al. compared placebo with 12 g infusion over 3 days in 110 patients and reported higher risk of death in the pralidoxime group. They concluded that there was no role for pralidoxime and it caused more harm than benefit (18). In another placebo controlled study by Cherian et al. pralidoxime doses of 4 g/day and 12 g infusion/day were compared with each other and with placebo. They found no difference with respect to mortality, ventilator requirement and atropine dosage (19). A meta-analysis by Peter et al. was not in favor of using pralidoxime for OP poisoning (11). They found that there was no effect of oxime treatment on mortality, ventilator requirement or intermediate syndrome .They even warned against use of oximes (11).

There are probable reasons for ineffectiveness of pralidoxime in the mentioned studies. Firstly, most of the studies were underpowered. Many studies did not include analysis of the nature of the OP compound, whether it was dimethyl or diethyl compound. In dimethyl OP poisoning, early aging of phosphorylated acetyl cholinesterase occurs making them resistant (8,15). Inclusion of more cases poisoned with the dimethyl group could have tilted the results against pralidoxime. Oximes are more useful when administered within 12 hours of poison ingestion; however, there were delays in pralidoxime therapy in some of the above-mentioned trials (17,18). In some trials, a low dose of pralidoxime were administered and the optimal therapeutic level of pralidoxime of 4 mg/ml may not have been achieved (17,18). Proponents of oximes, including the WHO, believe that the doses used in many trials were too low to be effective (20). In some studies pralidoxime was administered at a rapid rate (11,15). Rapid administration of oximes may induce tachycardia, laryngospasm, muscle rigidity, muscle weakness, neuromuscular blockade and central respiratory depression (21-23). These adverse effects of pralidoxime might have resulted in poorer final outcomes.

Eddelston, in a recent randomized controlled trial of 235 patients, compared WHO regimen with placebo (20). Mortality was found to be non-significantly higher in pralidoxime group. Need for intubation was similar in both groups. There was no difference between chlorpyrifos and

dimethoate. It was observed that in spite of clear reactivation of acetyl cholinesterase no clinical benefit could be achieved (20). They postulated that co-formulants in generic OP compounds could be a significant component of the toxicity which can detract from the efficacy of pralidoxime (20).

On the other hand, several earlier studies have shown favorable results of pralidoxime in treatment of OP poisoning. A study by Zheng et al. in which 46 patients were studied, revealed that higher doses of pralidoxime via infusion were superior with a lower mortality rate (24). Singh et al. in their study of 16 patients showed effectiveness of higher doses of pralidoxime (25). A Cochrane review by Eddelston et al. in 2002 questioned the validity of the methodology of earlier trials and stood out against pralidoxime therapy (10). On the other hand, a systematic review by Bairy et al. did not give a negative verdict on pralidoxime therapy. However, it was mentioned that the clinical benefits of pralidoxime were unclear (26). In addition, a systematic review by Buckley et al. concluded that available evidences were insufficient to indicate whether oximes are harmful or beneficial (27).

Further support for the effectiveness of pralidoxime has come from the study by Pawar et al. (13). They administered pralidoxime at a greatly higher dose than recommended by WHO for moderately sever poisoning (1 g continuous infusion every hour for 48 hours vs. 1 g bolus every 4 hours for 48 hours), and found significant benefit for the study group in terms of lower intubation rates, lower atropine requirement, shorter duration of ventilator support and lower mortality (13). The explanation for the excellent mortality rate and intubation outcomes for study group in the Pawar trial could be that their study was carried out in a professional center exclusively dealing with OP poisoned patients and mean time interval between admission to hospital and commencement of pralidoxime therapy was considerably short. Moreover, they included only moderately severe cases (13). Although Pawar's regimen has been proven effective, it is very expensive because it entails administration of very high doses of pralidoxime, a costly drug in most developing countries. Hence, a study comparing high dose regimen of Pawar et al.'s study with the WHO regimen is necessary to ascertain which of them is more cost-beneficial.

LIMITATIONS

The value of findings of the present study was limited by following factors. The details of the OP pesticide type (dimethyl or diethyl) in several patients could not be identified. Hence, subgroup analysis on any subgroup of OP compounds to find which of them has a better response to pralidoxime therapy could not be performed. Serum concentration of OP compound, serum pralidoxime levels and AChE activity could not be measured due to lack of facilities, while results of these parameters would have helped in an improved evaluation of the efficacy of pralidoxime.

In this study, instead of pralidoxime chloride, pralidoxime iodide was used which is about 30% lower dose than its chloride salt. This may have affected the comparison between the two regimens.

In this study, there was no blinding and allocation concealment, though the groups were age and gender matched. Since a placebo arm was not part of this study, it was not possible to disregard conclusions on the possibility of unusefulness of pralidoxime.

Further large-scale studies specifically designed to investigate subgroups of OP poisons such as diethyl and dimethyl derivatives are required to identify responsiveness of specific OP compounds to pralidoxime. Studies evaluating other oximes such as obidoxime and trimedoxime are needed as well.

CONCLUSION

A dose regimen of pralidoxime consisting of 2 g pralidoxime bolus followed by 8mg/kg/h infusion reduces morbidity and mortality in moderate cases of OP poisoning. The WHO dose regimen had significantly better outcomes compared to standard dose regimen. However, since this study is constrained with several limitations, it lacks strong conclusive data pointing to superiority of WHO regimen. Further large-scale studies are required to evaluate the two regimens.

ACKNOWLEDGEMENTS

We gratefully acknowledge the support of unit chiefs of all medical units in JSS Hospital. We wish to thank Prof. Lancy D'Souza, University of Mysore for statistical analysis.

Conflict of interest: None to be declared
Funding and support: None

REFERENCES

1. Clark RF. Insecticides: Organic Phosphorus Compounds and Carbamates. In: Flomenbaum NE, Goldfrank LR, Hoffman RS, Howland MA, Lewin NA, Nelson LS, editors. Goldfrank's Toxicologic Emergencies. 8th ed. New York: McGraw-Hill; 2006. p.1497-512.
2. Jeyaratnam J. Acute pesticide poisoning: a major global health problem. World Health Stat Q 1990;43(3):139-44.
3. Eddleston M. Patterns and problems of deliberate self-poisoning in the developing world. QJM 2000;93(11): 715-31.
4. Prajapati T, Prajapati K, Tandon R, Merchant S. Acute Chemical and Pharmaceutical Poisoning Cases Treated in Civil Hospital, Ahmedabad: One year study. Asia Pac J Med Toxicol 2013;2(2):63-7.
5. Prasad DRMM, Jirli PS, Mahesh M, Mamatha S. Relevance of Plasma Cholinesterase to Clinical Findings in Acute Organophosphorous Poisoning. Asia Pac J Med Toxicol 2013; 2(1): 23-7.
6. Singh S, Sharma N. Neurological syndromes following organophosphate poisoning. Neurol India 2000;48(4): 308-13.
7. Chugh SN, Aggarwal N, Dabla S, Chhabra B. Comparative evaluation of atropine alone and atropine with pralidoxime (PAM) in the management of organophosphorus poisoning. J Indian Acad Clin Med 2005;6:33-7.
8. Eyer P. The role of oximes in the management of organophosphorus pesticide poisoning. Toxicol Rev 2003;22(3):165-90.

9. Eyer P, Buckley N. Pralidoxime for organophosphate poisoning. Lancet 2006;368(9553):2110-1.
10. Eddleston M, Szinicz L, Eyer P, Buckley N. Oximes in acute organophosphorus pesticide poisoning: a systematic review of clinical trials. QJM 2002;95(5):275-83.
11. Peter JV, Moran JL, Graham P. Oxime therapy and outcomes in human organophosphate poisoning: an evaluation using meta-analytic techniques. Crit Care Med 2006;34(2): 502-10.
12. Rahimi R, Nikfar S, Abdollahi M. Increased morbidity and mortality in acute human organophosphate-poisoned patients treated by oximes: a meta-analysis of clinical trials. Hum Exp Toxicol 2006;25(3):157-62.
13. Pawar KS, Bhoite RR, Pillay CP, Chavan SC, Malshikare DS, Garad SG. Continuous pralidoxime infusion versus repeated bolus injection to treat organophosphorus pesticide poisoning: a randomised controlled trial. Lancet 2006;368(9553): 2136-41.
14. Senanayake N, de Silva HJ, Karalliedde L. A scale to assess severity in organophosphorus intoxication: POP scale. Hum Exp Toxicol 1993;12(4):297-9.
15. Varghese MJ, Agrawal A. Ideal dose of Pralidoxime in organophosphorus poisoning: Do we have an answer yet? Postgraduate Medicine (API & ICP) 2009;23:391-6.
16. de Silva HJ, Wijewickrema R, Senanayake N. Does pralidoxime affect outcome of management in acute organophosphorus poisoning? Lancet 1992; 339(8802): 1136-8.
17. Johnson S, Peter JV, Thomas K, Jeyaseelan L, Cherian AM. Evaluation of two treatment regimens of pralidoxime (1 gm single bolus dose vs 12 gm infusion) in the management of organophosphorus poisoning. J Assoc Physicians India 1996; 44(8):529-31.
18. Cherian AM, Peter JV, Samuel J, Jaydevan R, Peter S, Joel S, et al. Effectiveness of P2AM in the treatment of organophosphorous poisoning, a randomized double blind placebo controlled clinical trial. J Assoc Phys India 1997; 45(1):22-4.
19. Cherian MA, Roshini C, Visalakshi J, Jeyaseelan L, Cherian AM. Biochemical and clinical profile after organophosphorus poisoning--a placebo-controlled trial using pralidoxime. J Assoc Physicians India 2005; 53:427-31.
20. Eddelston M, Eyer P, Worek F, Juszczak E, Alder N, Mohamed F, et al. Pralidoxime in acute organophosphorous insecticide poisoning--a randomized controlled trial. PLoS Med 2009;6(6):e1000104.
21. Bevan M. Proposal for Inclusion of Pralidoxime in the List of Essential Medicines. Geneva: 17th Expert Committee on the Selection and Use of Essential Medicines (WHO EML). Pralidoxime Report. 2008.
22. Karalliedde L, Senanayake N. Organophosphorus insecticide poisoning. Br J Anaesth 1989;63(6):736-50.
23. Taylor P. Anticholinesterase Agents. In: Hardman JG, Limbird LE, Gilman AG, editors. Goodman & Gilman's The Pharmacological Basis of Therapeutics.10th ed. New York: McGraw-Hill; 2001. p.175-92.
24. Zheng G, Song S, Li M. Comparison on effects between concentrated-dose and non-concentrated-dose pralidoxime chloride on respiratory muscle paralysis in acute organophosphorous pesticide poisoning. (In Chinese) Zhonghua Nei Ke Za Zhi 2000;39(10):655-7.
25. Singh S, Chaudhry D, Behera D, Gupta D, Jindal SK. Aggressive atropinisation and continuous pralidoxime (2-PAM) infusion in patients with severe organophosphate poisoning: experience of a northwest Indian hospital. Hum Exp Toxicol 2001;20(1):15-8.
26. Bairy KL, Vidyasagar S, Sharma A, Sammad V. Controversies in the management of organophosphate pesticide poisoning. Indian J Pharmacol 2007; 39(2):71-4.
27. Buckley NA, Eddelston M, Li Y, Bevan M, Robertson J. Oximes for acute organophosphate pesticide poisoning. Cochrane Database Syst Rev 2011;(2):CD005085.