ORIGINAL ARTICLE

Effectiveness of High Dose Pralidoxime for Treatment of Organophosphate Poisoning

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Abstract

Background: For effective treatment of organophosphate (OP) poisoning, development of a standardized protocol with flexible dose regimen for atropine and pralidoxime is an essential step. In this study, we aimed to assess the protocol devised in our setting; Bach Mai Hospital Poison Treatment Center, for treatment of OP poisoning that included a higher dose regimen of pralidoxime (2PAM).
Methods: A protocol for treatment of OP poisoning was developed during 1995 to 1996, which included an atropinization scoring scale and a modification of 2PAM dose regimen. In this study, OP poisoned patients who were treated during 1997 to 2002 with the new protocol (study group or cases) were compared with historical control group which included OP poisoned patients treated between 1993 and 1994 prior to establishment of the new protocol.
Results: One-hundred and eight cases and 54 controls were included. The cases and controls were not significantly different according to age, gender and plasma cholinesterase activity on admission from each other. There was no significant difference of mean duration of 2PAM therapy between the two groups. The controls received mean total 2PAM dose of 7.2±4.1 g, while the patients in the study group received 20.0±12.7 g which was 2.77 times higher than the dose for control group (P<0.001). Patients in the study group received significantly lower doses of atropine (100.2±119.1 vs. 231.8±225.5, P<0.001). Patients in the study group required a shorter duration of hospital stay compared to controls (6.2±4.8 vs. 8.2±5.8, P=0.035). In addition, morality rate decreased significantly (P=0.004) from 13% to 1.9% by application of the new protocol.
Conclusion: The new protocol was more effective for patients with OP toxicity as it reduced the morbidities and mortality. A flexible regimen of 2PAM therapy for OP poisoning is recommended to be implemented.

Keywords: Atropine; Clinical Protocols; Organophosphate Poisoning; Pralidoxime Compounds; Therapeutic Human Experimentation

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INTRODUCTION

Organophosphate (OP) compounds are the most common pesticides used for deliberate self-poisoning, especially in agricultural countries such as Vietnam (1-4). Annually, an approximate of three million patients with pesticide poisoning occurs worldwide and 80% of them are due to OP compounds with high mortality rate (1,5). In Vietnam, hundreds of OP poisoned patients are hospitalized annually with the mortality rate ranging between 9-13% (6).

For treatment of OP poisoning, systematic reviews show no evidence to conclusively support the efficacy of administration of oximes and even some scientists have concluded that the drug might be harmful (5,7). Nevertheless, this area has been difficult to assess for a number of reasons including wide range of doses of oximes used in previous clinical studies, patients exposed to different amounts of OP compounds and different types of OP compounds used. At an individual level, both kinetics and dynamics of oximes may vary depending upon the severity of poisoning (8,9).

In order to minimize variations in practice and to provide a severity-based adjustment of pralidoxime administration, development of a standardized protocol with flexible dose regimen for atropine and pralidoxime has been considered as an essential step (5,8). In this study, we aimed to assess the protocol devised in our setting; Bach Mai Hospital Poison Treatment Center (PTC), for treatment of OP poisoning that included a higher dose regimen of pralidoxime.

METHODS

Study design

This study was carried out at the Bach Mai PTC, a specialized service for poisoning with 35 beds located at Bach Mai Hospital (10). The Bach Mai University Hospital is a national tertiary hospital with 1000 beds.

A protocol for treatment of OP poisoning was developed based on our clinical experience from 1995 to 1996, which included an atropinization scoring scale (Table 1) and a modification of pralidoxime dose regimen. Prior to 1994, the mean dose of pralidoxime being administered to patients was 7 grams per day with 13% mortality (6). In 1995-6, we piloted a new regimen of a higher dose of pralidoxime which was associated with a reduced mortality to 5.5% (Due P. unpubl. data).

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Table 1. Atropinization Scoring Scale (ASS)

System organ	Effect of atropine	Score	Effect of overdosed atropine	Score
Skin	No paleness, warmth	1	Flushing	2
Pupil size	3 – 5 mm	1	> 5mm	2
Heart rate	80 – 120 bpm	1	> 120 bpm	2
Respiratory	No brochospasm No hypersecretion	1	Dried or no secretion (thick phlegm, dry mouth and no saliva)	2
Mental status	Normal	1	Hyperexcitablity or unconsciousness	2
Abdomen	Normal	0	Distension, absent bowel sounds	2
Urinary retention	None	0	Present	2
Total score		$\sum_1$		$\sum_2$

Total ASS = $\sum_{1+} \sum_2$:
ASS < 4: Insufficient atropine → atropine dose should be increased
ASS = 4 - 6: Atropinization → maintain the atropine dose
ASS > 6: Atropine overdose → atropine should be stopped or the dose should be decreased

In the present observational study, OP poisoned patients who were treated at Bach Mai PTC during 1997 to 2002 with the new protocol were included (study group). The study was approved by scientific and ethics council for doctoral thesis of Hanoi Medical University with specialized code of 3.01.31. Study group patients (cases) were eligible for inclusion if they had ingested OP compounds with laboratory confirmation of an OP compound identified in urine, serum or gastric fluid and had either 1 of the 2 following criteria: (a) development of a cholinergic crisis or (b) plasma cholinesterase (PChE) activity less than 50% of lower normal level (LNL). Cases were excluded if they had concomitant poisonings.

The data of cases were compared with historical control group which included acute OP poisoned patients treated within the same facility between 1993 and 1994 prior to establishment of the new protocol.

Laboratory tests

OP compounds were detected by thin layer chromatography and GC-MS in urine, serum or gastric fluid. Plasma cholinesterase (PChE) was measured every 12 hours by an automatic biochemical analyzer (Roche-Hitachi 912, Tokyo, Japan), using the method devised by Knedel and Bottger (11), and the normal limits of PChE were 5300 to 12700 U/L in 37°C. PChE activity (%) was calculated by the following formula: PChE (%) = Patient's PChE level / LNL× 100.

New treatment protocol

The treatment protocol developed in PTC included instructions for standard care, atropine dosage and pralidoxime dosage according to poisoning severity and PChE activity.

Standard care: All patients admitted within 6 hours of OP ingestion received gastric lavage followed by multiple dose of activated charcoal. If the patients were admitted between 6 and 24 hours post-ingestion, they were given charcoal without lavage. If dermal exposure was observed or suspected, all the clothes were replaced and the skin was washed with soap or shampoo and copious amount of water.

Atropine therapy: All patients were given 2-5 mg of intravenous (IV) atropine sulfate every 5 to 15 minutes until atropinization was achieved and then atropine was given subcutaneously or intravenously with doses and intervals depending on the patient's requirement. The patient's atropine requirement was evaluated and adjusted according to atropinization scoring scale (ASS) (Table 1). Atropine therapy was discontinued when the required dose declined to equal or less than 2 mg/24 hours.

Pralidoxime therapy: Chloride salt form of pralidoxime (2PAM) is available in our setting which is supplied in 500 mg/20 mL vials (Choongwae Pharma Corp., South Korea).

- **Initial dose of 2PAM**: 2PAM was administered according to the clinical severity of the poisoning (number of cholinergic crisis syndromes developed in a patient) as it is shown in table 2.

- **Maintenance dose of 2PAM**: After achieving atropinization, the maintenance dose was started and administered to the patient via continuous infusion. The dose of 2PAM was adjusted every 6-12 hours according to PChE activity at each time point and/or patient's required dose of atropine to maintain atropinization (Table 2).

Discontinuation of 2PAM was considered when required atropine was equal or less than 2 mg/day and PChE activity was over 50 % in an increasing manner.

Treatments administered for historical controls

Standard care and atropine dosage administered to controls were similar to cases. However, the dosage of 2PAM was different and it was determined differently. It was based on severity of poisoning, though the severity was scored according to a different method:

A patient would get 1 score for each of the following conditions: (a) Ingestion of large amount of OP compound (to drink directly from the 300-500 mL bottle of 20-50% solution of an OP compound, more than one mouthful to half a bottle), (b) delayed admission to hospital (over a day post-ingestion or unknown time of ingestion for an unconscious patient), (c) respiratory failure, (d) hypotension,

Table 2. Pralidoxime dose regimen for study group

Initial dose			
Grading	Number of syndromes in cholinergic crisis		Dose
Grade 1 (mild)	1 Syndrome		IV bolus 0.5g/5min, then IV infusion at rate of 0.25g/h
Grade 2 (moderate)	2 Syndromes		IV bolus 1g/10min, then IV infusion at rate of 0.5g/h
Grade 3 (severe)	3 Syndromes		IV bolus 1g/10min, then IV infusion at rate of 1g/h
Maintenance dose			
Grading	Required dose of atropine	PChE Activity (%)	Dose
Grade 1 (mild)	< 2mg/h	(20 – 50) %	0.125g/h
Grade 2 (moderate)	2-5 mg/h	[10 – 20] %	0.25 g/h
Grade 3 (severe)	> 5 mg/h	< 10 %	0.5 g/h

Table 3. Pralidoxime dose regimen for historical controlled group

Severity of poisoning		2PAM dose in each time-point (gram)					
		Day 1			Day 2	Day 3	Day 4
		admission	2nd 8 hrs	3rd 8 hrs			
Grade 1	1 score	0.5	0.5	0.5	1	1	1
Grade 2	2 scores	1	1	1	2	2	2
Grade 3	3 scores	1.5	1.5	1.5	3	3	3
Grade 4	≥ 4 scores	2.0	2.0	2.0	4	4	4

(e) coma. In addition, a patient would get 0.5 score for each of the following signs: (a) heart rate < 60 bpm, (b) paleness / coldness, (c) miosis, (d) hypersecretion (e) PChE < 50%.

Based on the total scores, the severity of poisoning was classified into four grades and 2PAM was administered with doses of 1 to 4 grams per day for 3 to 4 days via IV injection of 0.5 to 1 grams intermittently (Table 3).

Statistical analysis

Data were analyzed using SPSS for windows version 11.5 (SPSS Inc., Chicago, IL). The data are reported as mean and standard deviation (SD), and frequency. Student t-test and chi square test were used to compare means and proportions. P values of less than 0.05 were considered as significant.

RESULTS

Demographic characteristics

In this study, 108 cases (study group) were enrolled that 59.3% of them were men. The data of 54 patients as historical controls were also obtained from medical records by chart review. The cases and controls were not significantly different according to age, gender and PChE activity on admission from each other (Table 4). All subjects (cases and controls) were Vietnamese. OP compounds were detected in gastric fluid, urine, or blood of all 108 patients. The type of OP compound ingested could be identified in 61 patients (56.5%) by taking history and among them, 72.1% were highly toxic according to classification of world health organization, and 67.2% were among the compounds which can cause intermediate syndrome (Table 5) (12,13).

Dose and duration of 2PAM treatment

The comparison of dose and duration of 2PAM treatment for the study and control groups are shown in Table 6.There was no significant difference of mean duration of 2PAM therapy between the two groups (P = 0.949). The historical control patients received mean total 2PAM dose of 7.2 ± 4.1 g, while the patients in the study group received 20.0 ± 12.7 g (range: 0.5 - 54) which was 2.77 times higher than the dose for control group (P < 0.001). Based on clinical severity, patients with grade 2 and 3 in the study group received significantly higher doses of 2PAM compared to their counterparts in control group (P = 0.016, < 0.001 respectively). However, the 2PAM dose was not significantly different between cases and controls with grade 1 severity. PChE reactivated in the study group relatively quick at a mean rate of 8.9 ± 14.2% per day.

Other treatments in the protocol and outcomes

Patients in the study group received significantly lower doses of atropine (100.2 ± 119.1 vs. 231.8 ± 225.5 mg, P < 0.001). Moreover, rate of OP toxicity complications including intermediate syndrome and paralysis in cases were significantly lower than controls (P = 0.011, 0.013, respectively). Duration of paralysis and the need for mechanical ventilation were significantly lower in cases compared to controls (P = 0.027, 0.025, respectively). Patients in the study group required a shorter duration of hospital stay compared to controls (6.2 ± 4.8 vs. 8.2 ± 5.8, P = 0.035). In addition, the morality rate decreased significantly (P = 0.004) from 13% to 1.9% by application of the new protocol (Table 7).

Table 4. Demographic and baseline characteristics of study and control groups

	Study group (n = 108)	Control group (n = 54)	P value
Age (years), mean ± SD	29.5 ± 14.2	25.5 ± 10.0	0.630
Gender, n (%)			
Male	64 (59.3)	30 (55.6)	0.498
Female	44 (40.7)	24 (44.4)	
PChE activity* (%), mean ± SD	22.8 ± 37.6	29.8 ± 26.8	0.230

* On admission

Table 5. Organophosphate compounds identified from patients in the study group

Compound	n (%)
WHO toxicity class I	44 (72.1)
Methamidophos (Monitor)*	33 (54.1)
Methidathion(Supracid)	4 (6.6)
Wofatox (Metaphos)*	3 (4.9)
Monocrotophos*	2 (3.3)
Diclorovos (DDVP)	2 (3.3)
WHO toxicity class II	16 (26.2)
Trichlorfon (Dipterex)	4 (6.6)
Dimethoate (Bi58)*	3 (4.9)
Fenitrothion (Ofatox)	2 (3.3)
Phenthoate	2 (3.3)
Edifenphos	3 (4.9)
Diazinon (Basudin)	2 (3.3)
WHO toxicity class III	1 (1.6)
Acephat	1 (1.6)

* OP compounds capable of causing intermediate syndrome

Adverse effects of 2PAM in the study group

Adverse effects of the new 2PAM dosage were minimal and found in 4 patients (3.7%). These included tachycardia (> 150 beats/min), recurrence of fasciculation or muscarinic symptoms, paralysis and hypertension. All adverse effects improved rapidly after discontinuation of 2PAM.

DISCUSSION

Treatment with oximes for OP poisoning has always been controversial. The effectiveness or futility of this treatment has attracted much debate. Some experts are not in favor of this treatment as they rely on studies that showed ineffectiveness or even harmfulness of the drug to the treated patients (14,15). Nevertheless, it has been ascertained that oximes can accelerate cholinesterase reactivation in OP poisoned patients (15,16).

For OP poisoning, atropine and pralidoxime are the two known specific antidotes (15). The use of atropine seems to be much easier because signs of atropinization are easier to be judged by the clinicians. Yet, for the oximes no clear endpoint showing adequate dose of the drug has been found, so far. To give appropriate dose of pralidoxime to a patient, it would be better to determine the dose according to the severity of OP poisoning. Besides, measurement of blood concentration of OP compound is not feasible in most medical settings and if available it often takes long time, hence useless for decision making and management of the patients. To date, clinical criteria and cholinesterase level have been used to estimate the severity of OP poisoning, though there is no consensus on their value (17,18).

In the present study, both clinical criteria (number of cholinergic crisis syndromes and patient's required dose of atropine) and PChE activity were used to classify the OP poisoned patients for receiving the appropriate dose of 2PAM. In the new protocol, initial dose of 2PAM was adjusted according to severity of poisoning and maintenance dose was adjusted according to patient's response to treatment (PChE activity and need for atropine). In other words, the new protocol includes flexible dose regimen of 2PAM according to the severity of OP toxicity and patient's therapeutic response. On the other hand, in the previous protocol (administered to historical control group), 2PAM was given in fixed doses for 4 days regardless of the patient's response. Therefore, in comparison to controls, cases (especially with moderate and severe toxicity) received higher doses of 2PAM and had better outcomes including lower dose and shorter duration of atropine therapy, lower rate of intermediate syndrome, lower rate of and shorter duration of paralysis, lower rate and shorter duration of mechanical ventilation, shorter duration of hospitalization and lower mortality rate. Greater effectiveness of higher doses of pralidoxime has also been shown in randomized studies (3,19) (Table 8). Mahesh et al., and Pawar et al. found that patients receiving higher doses of 2PAM experienced lower rates of intermediate syndrome, needed less assisted ventilation, required lower doses of atropine, and survived more (3,19). Shivakumaret al. also reported similar results in a non-randomized study comparing the high and low doses of 2PAM (20).

In contrast, the effectiveness of 2PAM in OP poisoning has been questioned when 2PAM-treated patients were compared with placebo patients (7,21). Eddleston et al. and Cherian et al. showed that administration of 2PAM would not provide a patient with any additional advantage

Table 6. Dose and duration of 2PAM treatment for study and control groups

	Study group (n = 108)	Control group (n = 54)	P value
Duration of pralidoxime therapy (day), mean ± SD	3.3 ± 1.7	3.3 ± 1.3	0.949
Total dose of pralidoxime (g), mean ± SD			
All patients	20.0 ± 12.7	7.2 ± 4.1	< 0.001
Grade 1 (mild)	8.0 ± 6.8	7.2 ± 3.7	0.611
Grade 2 (moderate)	17.9 ±10.8	7.4 ± 3.9	0.016
Grade 3 (severe)*	26.8 ± 11.3	7.2 ± 5.2	< 0.001
Comparison of different grades (1 vs. 2 vs. 3), P value	< 0.001	0.994	

* Grade 3 in study group equals to grade 3 and 4 in control group

Table 7. Outcomes in study and control groups

	Study group (n = 108)	Control group (n =54)	P value
Total dose of atropine (mg), mean ± SD	100.2 ± 119.1	231.8 ± 225.5	< 0.001
Duration of atropine therapy (day), mean ± SD	3.0 ± 2.0	6.1 ± 3.7	< 0.001
Intermediate syndrome, n (%)	2 (1.9)	6 (11.1)	0.011
Paralysis, n (%)	37 (34.3)	29 (53.7)	0.013
Duration of paralysis (day), mean ± SD	4.3 ± 3.6	6.7 ± 4,4	0.027
Mechanical ventilation, n (%)	47 (43.5)	32 (59.3)	0.025
Duration of mechanical ventilation (day), mean ± SD	4.4 ± 4.0	6.2 ± 4.9	0.096
Hospitalization (day), mean ± SD	6.2 ± 4.8	8.2 ± 5.8	0.035
Death, n (%)	2 (1.9)	7 (13.0)	0.004

compared to placebo (7,21). Even, Eddleston et al. demonstrated that death rate was significantly higher among patients receiving 2PAM compared to placebo (7). Sungur et al. similarly showed that death rate was higher in patients who received 2PAM compared to those who did not because of a national shortage of 2PAM in Turkey (22). Furthermore, in one study by Johnson et al. patients who received 12 g 2PAM had worse outcomes with higher mortality than controls who received 1 g 2PAM (23). It should be noted that in all these studies (7,21-23), the mean total daily dose of 2PAM was approximately 12 g or less, and so the effect of higher doses was not analyzed. However, in the present study (~20 mg/day) and the studies by Mahesh et al. (14.4 g/day for an average adult weight of 75 kg) and Pawar et al. (24 g/day for the first two days), higher doses of 2PAM were administered resulting in better outcomes.

Altogether, the findings of our study and the mentioned studies show that higher doses of 2PAM are more effective in terms of saving more lives, reduction of need for mechanical ventilation and decrease in OP poisoning related complications (3,19,20), though non-administration of 2PAM may not expose the OP poisoned patients to risk, as ascertained in other studies (7,21-23).

In order to get better effects from 2PAM therapy, it would be prudent to classify the patients according to the severity of poisoning. In addition, it is recommended that future trials for effectiveness of pralidoxime be performed with three arms, placebo, high dose (fixed regimen) and severity-based dose (flexible regimen), to accurately delineate usefulness of this medication for OP poisoning.

LIMITATIONS

The results presented in this article belong to 12 years ago. However, no change in the protocol, availability of 2PAM and hospital facilities has occurred, till date. In that sense, the results are still defensible. In addition, in this study, the data of study group were compared with historical controls. This may expose findings of the controls to bias of inaccurate recording of patients' characteristics and clinical manifestations.

CONCLUSION

A flexible dose regimen of 2PAM was effective especially for patients with moderate and severe OP toxicity as it reduced the morbidities and mortality. The flexible regimen of 2PAM therapy for OP poisoning is recommended to be implemented.

Table 8. Comparative studies done on effectiveness of pralidoxime therapy for organophosphate poisoning

Reference no., author(s), year	Randomization	Pralidoxime Dose plan	Mean total dose of pralidoxime (g)	Intermediate syndrome (%)	Assisted ventilation rate (%)	Atropine (mg)	Mortality rate (%)
3, Mahesh et al., 2009-2012	Case	2 g bolus + 8mg/Kg/h infusion for 5 days	NS	0	32.4	Mean ± SD: 345.0 ± 90.6	10.8
	Control	2 g bolus + 1g/6 h infusion for 5 days	NS	33.3	48.8	Mean ± SD: 933.1 ± 162.3	22.2
7, Eddleston et al., 2004	Case	2 g in 20 min, 0.5 g/h infusion for up to 7 days	NS	NS	21.5	NS	24.8
	Control	Placebo (Saline)	NS	NS	21.1	NS	15.8
19, Pawar et al., 2000-2003	Case	2 g in 30 min + 1 g/h infusion for 48 hours + 1 g/4h until weaning from ventilator	NS	NS	64	Median (IQR): 6 (4-6)	1
	Control	2 g in 30 min + 1 g bolus q4h for 48 hours + 1 g/4 h until weaning from ventilator	NS	NS	88	Median (IQR): 30 (25-45)	8
21, Cherian et al., 2005	Case	Severe poisoning: 12 g/day infusion for 3 days Moderate poisoning: 4 g /day for 3 days	12 for severe cases 4 for moderate cases	NS	70	Mean ± SD: 120.7 ± 158.8	10
	Control	Placebo (Saline)	0	NS	36.3	Mean ± SD: 108.5 ± 116.0	9.1
23, Johnson et al., 1996	Case	12 g infusion for 4 days	12	56	66.7	Mean ± SD: 44.2 ± 40.0 mg/day	22.2
	Control	1 g bolus	1	35.1	45.9	Mean ± SD: 42.7 ± 41.6 mg/day	13.9
Present study, Due P., 1997-2002	Case	0.5-1 g/5-10min + 0.25-1 g/h according to severity grading until atropine is needed < 2 mg/day and PChE > 50 %	20.0 ± 12.7	1.9	43.5	Mean ± SD: 100.2 ± 119.1	1.9
	Control	1-4 g/day for up to 3-4 days according to severity grading	7.2 ± 4.1	11.1	59.3	Mean ± SD: 231.8 ± 225.5	13.0

NS: Not stated --- IQR: Interquartile range

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