Comparison of Single-Dose Pralidoxime and Pralidoxime Infusions for the Treatment of Organophosphate Poisoning

Organofosfat Zehirlenmesinin Tedavisinde Tek Doz Pralidoksim ile Pralidoksim İnfüzyonunun Karşılaştırılması

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Geliş Tarihi/*Received:* 22.06.2011
Kabul Tarihi/*Accepted:* 29.11.2011

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ABSTRACT Objective: Organic phosphates (OP) bind covalently to acetylcholinesterase (AChE) and acetylcholine (Ach) accumulates in the synaptic cleft. Administering oximes before aging process causes breakage of the covalent bond between OP-AChE, and allows reactivation of AChE. Pralidoxime (PAM) is the most commonly used oxime. The purpose of this study is to determine the best PAM regimen for the length of hospitalization, the need for mechanical ventilation and reduction of the duration of mechanical ventilation in patients presenting with OP poisoning. **Material and Methods:** Thirty four patients included in this study were organized according to the order of enrollment, randomized and divided into two groups. Seventeen patients in the group I were given a single dose of 2 g/20 min PAM infusion (bolus dose), while 17 patients in group II were administered a dose of 2 g/20 min followed by 6 g/24 hours PAM infusion (bolus and infusion). Clinical signs and symptoms as well as the serum butyrylcholinesterase (BCHE) levels were used to verify the patients' diagnoses. **Results:** There were no significant differences between the groups. **Conclusion:** We suggest that PAM bolus plus infusion therapy does not have any advantage over a single dose of bolus PAM therapy the in treatment of OP poisoning.

Key Words: Pralidoxime; poisoning; cholinesterase reactivators

ÖZET Amaç: Organik fosfatlar (OP) asetilkolinesteraza (AChE) kovalent olarak bağlanır ve sinaptik aralıkta asetilkolin (Ach) birikir. Süreç gelişmeden önce oksim uygulanması OP ile AChE arasındaki kovalent bağı kırar ve AChE'nin reaktivasyonuna izin verir. Pralidoksim (PAM) en sık kullanılan oksimdir. Bu çalışmanın amacı OP zehirlenmesi semptomlarıyla gelen hastalarda hastanede kalış süresinin uzunluğu, mekanik ventilasyon ihtiyacı açısından en iyi PAM rejimini belirlemek ve mekanik ventilasyonun süresini azaltmaktır. **Gereç ve Yöntemler:** Bu çalışmaya alınan 34 hasta kayıt sırasına göre organize edildi ve rastgele iki gruba ayrıldı. Grup I'deki 17 hastaya tek doz 2 g/20 dak PAM infüzyonu (bolus dozu) verildi, grup II'deki 17 hastaya 6 g/24 saat PAM infüzyonundan sonra 2 g/20 dak PAM infüzyonu yapıldı (bolus+infüzyon). Hastaların tanısını doğrulamak için serum butitilkolinesteraz (BCHE) düzeylerinin yanısıra klinik belirti ve bulgular kullanıldı. **Bulgular:** Gruplar arasında anlamlı fark yoktu. **Sonuç:** OP zehirlenmesinin tedavisinde PAM bolus+infüzyon tedavisinin tek doz bolus PAM tedavisine göre herhangi bir avantajı olmadığını düşünüyoruz.

Anahtar Kelimeler: Pralidoksim: zehirlenme; kolinesteraz reaktivatörleri

Turkiye Klinikleri J Med Sci 2012;32(2):472-7

Organic phosphate (OP) compounds are widely used as insecticides all over the world. These compounds are easily obtained because of their extensive use in agriculture, lack of supervision during their use and their cheap cost. Due to the ease of access, OP overdose due to ac-

doi: 10.5336/medsci.2011-24589

cidental poisoning or suicidal intake is relatively common in our country. OP poisoning affects all vital functions and can cause death if treatment is delayed. Thus, early diagnosis and treatment increases the chance of saving lives.[1-3]

Organic phosphates affect the nervous system by binding covalently to acetylcholinesterase (AChE), leading to the accumulation of acetylcholine (Ach) in the synaptic cleft. This condition results in clinical symptoms in the central and peripheral nervous system and, is called as cholinergic crisis. Patients with OP poisoning are monitored in the intensive care unit and may require mechanical ventilation. Patients on ventilators may encounter serious problems due to the mechanical ventilation process.[1,2]

The OP-AChE bond becomes irreversible after one phosphorous leaves the OP molecule. This condition is called "aging". As aging progresses, the activity of the cholinesterase enzyme deteriorates irreversibly. Administering oximes before aging process causes breakage of the covalent bond between OP-AChE and allows reactivation of AChE. Pralidoxime (PAM) is the most frequently used oxime. In order to be effective before aging develops, it should be administered within 24-36 hours of OP poisoning. Furthermore, PAM cannot pass the blood-brain barrier because of its quaternary ammonium shape and low lipid solubility. Thus, PAM exerts its main effects on the peripheral nervous system, particularly in the neuromuscular junction.[3-9]

The recommended dose of PAM is 25-50 mg/kg (1-2 g) intravenously with slow administration (15-30 min). In addition, it was also reported to be given by continuous infusion of 25-50 mg/kg/hour (maximum 500 mg/kg/sec) after a 1-2 g of loading dose.[10] However, the ideal PAM dose scheme has yet to be identified. The purpose of this study is to determine the length of hospitalization, the need for mechanical ventilation and the regimen of PAM infusion which is best to reduce the duration of mechanical ventilation in patients presenting with OP poisoning symptoms.

MATERIAL AND METHODS

This study have been conducted prospectively between March 2004 and September 2005, after the approval of Ethics Committee by enrolling the patients who applied to the emergency unit of Cukurova University, Faculty of Medicine with OPi intoxication.

Patients who were poisoned or committed suicide with an OP-containing medicine, administered subcutaneously, orally or via injection; who had OP poisoning symptoms, and whose relatives brought in a drug container that had an information sheet describing the contents of the drug were included in this study. Patients who were poisoned with carbamate compounds or patients who had received treatment prior to arriving at our facility were not included. During the study, 89 patients with OP poisoning admitted to the emergency. After the evaluation, 25 of these patients were excluded because they had received treatment before arriving our hospital, 23 patients were excluded because we could not obtain the content of the drug used, and seven patients were excluded from the study because of carbamate poisoning. Clinical signs and symptoms as well as the serum butyrylcholinesterase (BCHE) levels were used to verify the patients' diagnoses.

In all patients, The treatment started immediately. Following a detailed neurological examination, the consciousness state of the patient was evaluated using the Glasgow Coma Scale (GCS). Patients who had an insufficient respiration, an O_2 saturation≤90% as measured by a pulse oximeter and a GCS ≤8 were intubated and supported by mechanical ventilation. A daily dose of 3000 mL/m^2 saline and 5% dextrose solution were administered. Gastric lavage was performed through a gastric wh,ch was followed by administration of activated charcoal. A urinary catheter was inserted and fluid replacement was given based on the urine excretion. After venous introduction of atropine (atropinization), 1 mg/kg/day dose of continuous atropine infusion was administered until anticholinergic symptoms were observed in patients. The atropine infusion dose was regulated accord-

ing to the patient's cholinergic symptoms. After the respiratory functions of intubated patients improved, mechanical ventilation was discontinued and there was no need for further mechanical ventilation in the follow-up period.

Thirty four patients included in this study were organized according to the order of enrollment, randomized and divided into two groups. Seventeen patients in the group I were given a single dose of 2 g/20 min PAM infusion while 17 patients in the group II were administered 2 g/20 min PAM followed by 6 g/24 hours PAM infusion.

SAMPLE COLLECTION AND ANALYSIS

Immediately upon arrival, the patients' blood was drawn and a complete blood count (CBC) was obtained by the "automatic complete blood count" method using a LH 720 Beckman Coulter apparatus, and the BCHE serum levels were measured by the "Enzymatic Calorimetric Test" method using COBAS INTEGRA 800 Roche diagnostic apparatus at 2-8°C. Normal serum BCHE levels were 6400-15500 U/L.

STATISTICAL ANALYSIS

All data were evaluated using the statistical software SPSS version 14.0. Variables were expressed as mean±standard deviation (SD). Variables were analyzed using the Mann Whitney U test and Chi-Square tests to determine whether there were any significant differences. The significance level chosen was $p<0.05$. Data were presented as mean±SD, median, minimum (min) and maximum (max). Statistical power analysis is 0.8502.

RESULTS

There was no statistically significant difference between the groups with regard to age, gender, type of medicine that caused poisoning or the ways of poisoning (Table 1). Among patients who were included in the current study, seven were intubated and were connected to mechanical ventilation (three in group 1 and four in group 2). All patients had a GCS≤8 and were poisoned as a result of a suicide attempt. In addition, there was no significant difference in the serum BCHE levels between patients who were or were not intubated.

TABLE 1: Clinical characteristics and the poison used in group 1 and 2.

	Group 1	Group 2	p
Age (years)	21.7 ± 4.9	25.7 ± 6.1	0.062
Sex (female/male)	11/6	10/7	0.786
Suicidal/accidental	13/4	16/1	0.394
Arrival time (hour)*	5.4 ± 4.6	6.1 ± 6.8	0.786
Access way of the poison	Oral: 14 Subcutaneous injection:1 Respiration: 1	Oral:17	0.394
OP compounds			
Diazinon	10	7	>0.05
Diklorvos	3	5	>0.05
Chlorpyrifos	2	2	>0.05
Monocrotophos	1	1	>0.05
Metamidophos	1	1	>0.05
Paration	-	1	>0.05

* The time elapsed between the poisoning and arrival to the hospital,
OP: Organic phosphate.

There was no significant difference between the groups when the following variables were compared: time elapsed between the poisoning and arrival to the hospital, atropinization dose, the overall atropine dose and atropine treatment time. Moreover, the time to start oral feeding and the hospitalization time were also not significantly different (Table 2).

The initial serum BCHE levels were less than 3200 U/L in all patients in this study. Daily observations showed that there was no significant difference in the serum BCHE levels between the groups ($p<0.05$). Upon discharge, 12 patients from group 1 and 10 patients from group 2 had serum BCHE levels < 3200 U/L. All patients included in the current study were cured by the time they were discharged.

DISCUSSION

OP poisoning is a serious health concern especially in developing countries and has high morbidity and mortality rates if the treatment is delayed. Although in vitro studies show that oximes are effec-

TABLE 2: The treatments and outcomes of group 1 and 2.

		Grup 1	Grup 2	p
Atropinization dose (mg)	Mean±SD	115±188	157±307	0.946
	Median	40.00	50.00	
	Min-max	20-700	10-1300	
The overall atropine dose (mg)	Mean±SD	355±710	347±658	0.999
	Median	100.00	110.00	
	Min-max	40-2090	20-2650	
Atropine treatment time (hour)	Mean±SD	78±64	72±46	0.892
	Median	64.00	64.0	
	Min-max	8-258	20-216	
Switch to oral feeding time (hour)	Mean±SD	102±76	95±42	0.812
	Median	78.00	80.00	
	Min-max	33-336	54-232	
Total hospitalization time (hour)	Mean±SD	125±93	123±52	0.454
	Median	97.00	108.00	
	Min-max	38-432	63-288	

SD: Standard deviation.

tive in reactivating AChE previously inhibited by OP, oximes have a low affinity for the OP-AChE complex, so activated AChE can easily be re-inhibited by OP. When the OP-AChE complex is "aged", oximes have limited/no effect.[10] Thus, there is a controversy about whether oximes should be used as treatment for OP poisoning and if so, what the optimal dose is. A previous study found that after the intravenous administration of 1 g PAM IV bolus, the PAM serum levels quickly dropped below 4 microgram/mL within 1.5-2 hours, while continuous PAM infusion at the rate of 0.5 g/hour maintained the PAM serum levels at greater than 4 microgram/mL. Therefore, a continuous infusion of PAM was suggested to be a better treatment for acute OP poisoning.[11,12] In addition, in vivo studies suggested that the time elapsed between poisoning and oxime administration and the type of OP were very important.[9,13]

In the study by Jeong et al.,[14] it was found that patients receiving a high-dose infusion treatment had a shorter period of mechanical ventilation, a shorter duration of intensive care unit stay, and a faster plasma cholinesterase reactivation rate compared to the ones who had a low-dose infusion treatment. Additionally, another study showed that a more concentrated dose of PAM was more effective in treating OP-dependent respiratory muscle paralysis.[15]

Additionally, some clinical studies showed that using atropine and PAM versus atropine alone produced no significant effects on the development of the intermediate syndrome, mechanical ventilation requirement, the duration of mechanical ventilation support, intensive care unit stay and mortality. In addition, PAM did not decrease the amount of atropine used and the treatment time.[16-19] In a study on 72 patients with OP poisoning by Johnson et al.,[20] one group received a 1 g single dose of PAM (low-dose treatment group) and the other group received 12 g of PAM daily for four days (high-dose treatment group). It was observed that the patients in high-dose PAM treatment group needed respiratory support and developed intermediate syndrome more frequently when compared to the low-dose treatment group. In addition, subgroup analysis revealed that the patients who received PAM within 12 hours after poisoning were less likely to develop intermediate syndrome compared to patients receiving PAM 12 hours or more after poisoning. However, there was no difference in the rate of respiratory support required

by these groups. A randomized double-blind, placebo-controlled study by Eddleston et al. determined that particularly with the suicidal intake of high doses of OP, high dose pralidoxime treatment was not superior to placebo in terms of patient survival.[21]

Our study did not show any significant difference between the two groups for the need of mechanical ventilation and respiratory support time. Additionally, two groups did not have any significant difference in atropinization doses, overall atropine amount administered or the length of atropine treatment required. Moreover, there was no significant difference for transition to oral feeding and hospitalization time between two groups. None of the patients died and all of them were cured by the time of discharge from the hospital. The low mortality rate was associated with early diagnosis, prompt initiation of the therapy and accurate and continued administration of atropine.

The measurement of serum BCHE levels is frequently used to confirm an OP poisoning diagnosis. Several studies show that low serum levels of BCHE support the diagnosis of acute OP poisoning, but are not associated with the severity of symptoms, the need for respiration support, the duration of the intensive care unit stay, type l and type 2 paralyses, or mortality. Moreover, previous studies have shown that PAM does not change the serum BCHE levels.[17-19,22] Our study showed similar results and all our patients had serum BCHE levels <3200 U/L upon arrival to the hospital. There was no correlation between the need for mechanical ventilation and serum BCHE levels during follow-up. Additionally, the group that received PAM infusion did not differ from the group that received a single dose of PAM concerning serum BCHE levels.

In conclusion, we suggest that PAM infusion therapy does not have any advantage over a single dose PAM therapy, dose of atropine given or atropine treatment time. In addition, it does not have any effect on hospitalization times. Further investigations on larger case series are needed for more precise results.

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