Prognostic Factors of Organophosphate Poisoning Between the Death and Survival Groups

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In this prospective case series study, we consider the different factors between death and survival groups of organophosphate poisoning. Patients in tertiary-care medical center who had been exposed to organophosphate were included in the study. Pralidoxime (PAM) was discontinued after atropine had controlled the clinical situation. We recorded the demographic data, amount of organophosphate consumption, duration of coma, duration of ventilator use, duration of hospitalization, findings of chest X-ray, white blood cell count, acetylcholinesterase concentration, plasma cholinesterase concentration, total atropine amount, duration of atropine use, total PAM amount, duration of PAM use, urine organophosphate peak concentration, duration of urine organophosphate and mortality rate. Urine was collected every 8 hours and was analyzed by gas chromatography equipped with a flame photometric detector and gas chromatography with mass spectrometer detector for organophosphate determination. The urine organophosphate peak concentration was recorded. Wilcoxon rank sum test was used to compare the factors between death and survival groups. Fisher's exact test was used to compare the different findings of chest X-ray between the death and survival groups. Evidently, the death group had a higher amount of organophosphate consumption, duration of coma, and higher white blood cell count than those in the survival group. Also, the death group had lower duration of hospitalization, and decreased concentrations of acetylcholinesterase and plasma cholinesterase. Total PAM amount use and duration of PAM use were lower. However, the duration of ventilator use, findings of chest X-ray, total atropine amount, duration of atropine, urine organophosphate peak concentration and duration of urine organophosphate were similar in both groups. The mortality rate of our 50 cases was 20%. As stated earlier, the cases of the death group had insufficient PAM therapy. The maximum duration of PAM use was shorter than the maximum duration of urine organophosphate, although the medians of duration of PAM use were more than the medians of duration of urine organophosphate in both the survival and death groups. Prolonged coma duration, lower level of acetylcholinesterase and lower level of plasma cholinesterase were related to the poor prognosis of the patients.

Key Words: acetylcholinesterase, mortality, organophosphate, plasma cholinesterase, prognosis (*Kaohsiung J Med Sci* 2007;23:176–82)

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Organophosphates are widely used in agriculture. Reports from the National Poison Control Center of Taiwan indicate that organophosphate poisoning is the leading cause of poisoning [1]. The main types of poisoning are acute cholinergic crisis, intermediate

syndrome and delayed neuropathy [2,3]. Atropine and pralidoxime (PAM) are common antidotes used in Taiwan.

The action of PAM is to activate acetylcholinesterase by releasing acetylcholinesterase from acetylcholinesterase–organophosphate complex. It reduces the amount of atropine required [4,5]. It also modulates the nicotinic and central nervous system effects of organophosphates [6]. A report in the literature shows that organophosphate poisoning symptoms could reappear later following 1-day treatment with an oxime. The authors concluded that lipid-soluble and highly protein-bound organophosphates were retained in the tissues and their release later resulted in the reappearance of the symptoms of poisoning [4]. In our clinical presumption, the duration of atropine and PAM therapy should cover the reappearance of the symptoms of poisoning because of the release of organophosphate from the tissue. We collected urine containing organophosphate to ascertain whether the duration of PAM use can cover the duration of urine organophosphate in the same way as it covers the release of organophosphate from the tissue.

Some authors reported that serum cholinesterase concentration did not correlate with the total atropine amount used. In the acute phase of organophosphate poisoning, low serum acetylcholinesterase supports the diagnosis of organophosphate poisoning but it does not show a significant relationship with the severity of poisoning [7]. Serum cholinesterase levels have no prognostic value in acute organophosphate poisoning according to Nouira et al [8]. However, Brahmi et al reported that the marked decrease in acetylcholinesterase activity appears as a prognostic factor in acute organophosphate poisoning [9]. We compared the different factors including acetylcholinesterase concentration and plasma cholinesterase concentration between death and survival groups of organophosphate poisoning to determine the prognostic factors.

Materials and Methods

Clinical data collection

Organophosphate poisoning cases over a 2-year period were included in this study at Taichung Veterans General Hospital. The exact name of the organophosphate was determined. The demographic data, amount of organophosphate consumption, duration of coma, duration of hospitalization, duration of ventilator use, findings of chest X-ray, white blood cell count, acetylcholinesterase concentration, plasma cholinesterase concentration, total atropine amount use, duration of atropine use, total PAM amount use, duration of PAM use, urine organophosphate peak concentration, duration of urine organophosphate and the cause of mortality were recorded. The patient was first treated with atropine (50 μg/hour, keeping heart rate [HR] at 80–120 beats/minute) and PAM (0.5 g/hour continuous intravenous drip) until the symptoms subsided. If heart rate decreased or the rale/rhonchi of breathing sound increased, we increased atropine dosage and allowed the heart rate to reach not more than 120 beats/minute. If sudden onset of detrimental condition developed, bolus atropine was used. When the breathing sound was clear, atropine was tapered off and then discontinued. If there was no reappearance of symptoms, PAM was then discontinued.

Urine was collected from the patient every 8 hours and 10 mL was saved at –20°C in a freezer. It was then detected by gas chromatography equipped with a flame photometric detector (GC/FPD) and gas chromatography with mass spectrometer detector (GC/MS) for organophosphate determination. Then urine organophosphate peak concentration was recorded.

Urine samples analysis

Organophosphate pesticide preparations

A 5 mL sample of urine was added to 1 g of sodium chloride, mixed thoroughly, and extracted twice with 5 mL of methylene chloride. The extracts were combined and dried through Na_2SO_4 and evaporated to dryness. The residue was then dissolved in 0.5 mL of acetone [10].

Instrument

A Hewlett Packard 5890 series II GC/FDP was used for all measurements in organophosphate analysis. A DB-608 capillary column (30 m × 0.53 mm ID) was used. The column temperature was kept at 180°C for 10 minutes. Operation conditions were as follows: injection port temperature at 240°C, detector temperature at 250°C, carrier gas (N_2) flow rate of 10 mL/minute, H_2 flow rate of 75 mL/minute and air flow rate of 100 mL/minute. The organophosphates were identified by GC/MS. An HP-5MS capillary column (30 m × 0.25 mm ID) was used. The column temperature was kept at 60°C for 2 minutes and 30°C/minute

to 270°C for 10 minutes. Solvent delay was 3 minutes. Operation conditions were injection port temperature at 220°C, detector temperature at 280°C, carrier gas (He) flow rate at 1.0 mL/minute and electron impact at 70 eV.

Quantitative analysis

The quantitativeness of biologic samples was examined using GC/FPD. The detection limits in urine were 0.003 (o-ethyl-o-(4-nitrophenyl)-phenylphosphonothioate [EPN], parathion-methyl), 0.004 (demeton-S-methyl), 0.01 (acephate, methamidophos, mevinphos), 0.02 (diazinon, monocrotophos, parathion-ethyl) and 0.03 (chlorpyrifos, dimethoate, dipterex, ethion, fenitrothion, profenofos, phorate, prothiofos) μg/mL, respectively, at a signal to noise ratio of 3 (limit of quantitation, LOQ). The recovery range of 17 organophosphate pesticides at concentrations of 0.25, 0.5 and 1.0 μg/mL was 80.38% to 103.7% from spiked urine. Within-run study ($n=5$) of urine samples spiked with 0.25 μg/mL of 17 organophosphate pesticides gave the range of coefficients of variation (CV) from 0.76% to 7.08%.

Data description analysis

Due to small case numbers and nonparametric data, Wilcoxon rank sum test was used to compare the median data of the death and survival groups. Fisher's exact test was used to compare the different findings of chest X-ray between the death and survival groups.

Results

Table 1 shows the list of organophosphates in the 50 patients. Table 2 compares the data between the 40 survivors and the 10 dead. Thus, from the data in Table 2, the death group had a higher amount of organophosphate consumption, duration of coma and white blood cell count than those in the survival group. However, the findings of chest X-ray, duration of ventilator use, total atropine amount, duration of atropine, urine organophosphate peak concentration and duration of urine organophosphate were similar in both groups. The mortality rate was 20%. The reasons for death were cardiac arrest (6 cases), septic shock with aspiration pneumonia (2 cases), intractable pulmonary edema (1 case), and cardiogenic shock (1 case).

Table 1. List of organophosphates

Organophosphate	*n*
EPN	4
Dipterex	1
Diazinon	1
Dimethoate	2
Parathion-ethyl	2
Parathion-methyl	1
Profenofos	1
Monocrotophos	2
Mevinphos	10
Chlorpyrifos	3
Prothiofos	1
Ethion	1
Dimeton-S-methyl	1
Methamidophos	17
Phorate	1
Fenitrothion	1
Acephate	1

Discussion

There are significant differences between the death and survival groups in their amount of organophosphate consumption, duration of coma, duration of hospitalization, white blood cell count, concentrations of acetylcholinesterase and plasma cholinesterase, total PAM amount, and duration of PAM use as shown in Table 2. The death group had a relatively higher amount of organophosphate consumption, although there were variable chemical structures as shown in Table 1. Predicted mortality was not significantly different from Glasgow coma scales reported by Bilgin et al [11]. Duration of coma was significantly higher in the death group of this study. Prolonged coma duration was related to death. However, we should treat and cure the patients intensively in spite of coma, because the maximum duration of coma in the survival group was up to 20 days.

Mechanical ventilators were required by patients because of bronchial secretions, altered conscious level, pneumonia, flaccid paralysis and intermediate syndrome [12]. The indications for mechanical ventilator were encountered in each group. Mortality following organophosphate poisoning remains high despite adequate respiratory support, intensive care and specific therapy with atropine and oximes [13]. The duration of ventilator use was not different for both the groups of this study. The duration of ventilator use was not a prognostic factor in organophosphate poisoning.

Table 2. Comparisons between the death and survival groups

	Deaths ($n=10$)	Survivals ($n=40$)	p
Age (yr)			0.8938
Median	49	46	
Min–max	20–76	16–77	
Sex			0.2770
Male	5	28	
Female	5	12	
Amount of organophosphate consumption			0.0171*
Median	275	80	
Min–max	150–500	30–500	
Unknown	6	15	
White blood cell count (/mm^3)			0.0169*
Median	20,900	13,900	
Min–max	8,200–28,700	3,200–25,000	
Chest X-ray			0.051
Pulmonary edema	4	17	Fisher's
Pneumonia	4	4	exact
Normal	2	19	
Duration of coma (27 cases) (d)			0.0062†
Median	2	0	
Min–max	1–29	0–20	
Duration of ventilator use (32 cases) (d)			0.1834
Median	2.5	1.5	
Min–max	1–29	0–30	
Duration of hospitalization (d)			0.0139*
Median	2.5	8	
Min–max	1–29	2–50	
Acetylcholinesterase concentration (U/L)			0.0031†
Median	2,471	4,281	
Min–max	600–4,093	1,287–10,644	
Plasma cholinesterase concentration (U/L)			0.0079†
Median	1,375	2,455	
Min–max	500–4,608	937–8,663	
Total atropine amount use (mg)			0.2297
Median	4.02	2.53	
Min–max	1.20–38.71	0–137.63	
Duration of atropine use (d)			0.9513
Median	2.5	3	
Min–max	1–29	0–28	
Total PAM amount use (g)			0.0428*
Median	15.5	47.5	
Min–max	2–168	2–167.5	
Duration of PAM use (d)			0.0382*
Median	2.5	5.5	
Min–max	1–15	1–15	
Urine organophosphate peak concentration (ppm)			0.1235
Median	118	1.26	
Min–max	0.01–671.98	0.02–2,318.47	
Duration of urine organophosphate (d)			0.7181
Median	2	3	
Min–max	1–17	1–13	

*$p<0.05$ (Wilcoxon rank sum test); †$p<0.01$ (Wilcoxon rank sum test). Min = minimum; max = maximum; PAM = pralidoxime.

One-third of subjects needing mechanical ventilation and reaching intensive care units die within the first 72 hours of poisoning [13]. The duration of hospital stay was shorter in the death group than in the survival group of this study. The seven of the 10 deaths were caused by cardiogenic reasons. The reason was why the duration of hospital stay was shorter, but the duration of ventilator use was not related to death.

White blood cell count was elevated in the death group, which may be related to inflammation and lung infection. One cause of death was due to aspiration pneumonia. Aygun et al reported that low serum acetylcholinesterase supports the diagnosis of organophosphate poisoning but this does not show a significant relationship to the severity of poisoning. There was no significant difference between the first-day serum acetylcholinesterase of the patients with severe poisoning and of the patients with mild poisoning [7]. However, Brahmi et al reported that marked decrease in acetylcholinesterase activity appears as the prognostic factor in acute organophosphate poisoning [9]. There were lower concentrations of acetylcholinesterase and plasma cholinesterase in the death group than in the survival group of this study. These two factors were related to the clinical outcome of the patients in this study.

Because of the phenomenon of aging, oxime treatment must be started as early as possible after exposure, ideally within 5 minutes to 2 hours. Traditionally, a patient is treated with PAM for 1–2 days [5]. As a result, physicians are unable to treat seriously ill organophosphate poisoning patients with long-term treatment of PAM and have to use more atropine. This also indirectly lengthens the patient's hospital stay and affects the rate of recovery. The lipid-soluble and highly protein-bound organophosphates remaining in the tissues would cause reappearance of toxic and clinical symptoms [5]. PAM therapy should cover the reappearance of organophosphate from tissue and clinical symptoms. It is impossible to completely recover and prevent reappearance of symptoms with a 3-day PAM regimen. In this study, the maximum duration of PAM use was 15 days and the maximum duration of urine organophosphate was 17 days (Table 2), although the medians of duration of PAM use were more than the medians of duration of urine organophosphate in both the survival and death groups.

Atropine dosing should be titrated to the therapeutic end point of the clearing of respiratory secretions and the cessation of bronchoconstriction [14]. Atropine had beneficial effects on the heart rate, prolonged the time before the heart rate declined, and delayed death in a rat study [15]. In this study, death was mainly caused by cardiogenic deterioration. The total atropine amount use in the death group showed no difference from that in the survival group. Whether we augment atropine amount and duration of atropine use and set up the higher increase of heart rate range (for example 90–130 beats/minute), it can result in early decrease of bronchial secretion and lower mortality. Further controlled study is needed to verify this.

Clinical treatment with atropine and PAM should be continued until symptoms cease. If this is not done, there will be a detrimental effect on those patients whose urine organophosphate remains positive for longer periods of time and whose organophosphate concentrations are high. The death group had a greater amount of organophosphate consumption and a lesser total PAM amount use than that of the survival group. The median of total PAM amount use was 15.5 g and the median of the duration of PAM use was 2.5 days. The cases of the death group may have had insufficient PAM therapy compared with the maximum of PAM 12 g/day (500 mg/hour) [16]. Aggressively increasing the amount of PAM was suggested in the death group of this study. However, in a new meta-analysis of clinical trials, oximes were not effective in the management of organophosphate-poisoned patients and, surprisingly, they can be dangerous and worsen the patient's clinical situation. More research is needed to define the effect of PAM therapy [17].

Animal experiments show that organophosphates are detected in urine and feces from 24 hours to 3–4 days. Experimental oral administration of several other pesticides to human volunteers has shown that when urinary metabolites are measured, the rate of elimination is similar to that seen in animal studies. It appears that 90% of the compound is eliminated in between 6 and 24 hours after administration. There is evidence, however, that after self-poisoning, patients may still be excreting detectable urine levels of metabolites up to 14 days later [18]. This study determines the length of time in which organophosphates can be detected in the urine, which represents the relative length of time that organophosphates are retained in the body. When humans attempt suicide, they may take larger amounts of the poison and so urine samples remain positive for longer periods of time than

those of animals. In this study, the urine organophosphate peak concentration and duration of urine organophosphate were not definitely related to death under PAM and atropine therapy. However, the longest duration of detectable urine was 17 days and its highest concentration was 2,318.5 mg/mL (Table 2). The maximum durations of atropine use and of PAM use were 29 days and 15 days, respectively. In our clinical judgment, PAM and atropine therapy should cover the reappearance of organophosphate released from the tissue.

As shown in Table 2, our mortality rate for 50 cases was 20%. The reasons for death were cardiac arrest (6 cases), septic shock with aspiration pneumonia (2 cases), intractable pulmonary edema (1 case) and cardiogenic shock (1 case). Singh et al reported that the mortality rate of 18 patients with organophosphate poisoning was 22% [19]. The causes of death were intractable pulmonary edema (2 cases), cardiac arrhythmia (1 case) and aspiration pneumonia (1 case). Yamashita et al reported a mortality of 25% (32/130). The causes of death were delay in discovery and transport (18 cases), insufficient respiratory management (8 cases) and severe underlying or co-existing diseases (6 cases) [20]. We had a higher rate of cardiac arrest (6/10). Yamashita et al reported delay in discovery and transport (18/32). There might also have been delay in discovery of transient cardiac arrhythmia in this study with only cardiac arrest recorded. We had a similar mortality rate to the other reports.

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有機磷中毒個案死亡和存活者之預後因素

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我們的研究目的是比較有機磷中毒時死亡者和存活者之差異，在前瞻性連續個案收集之研究，將三級教學醫院有機磷中毒個案收錄在本研究中，當臨床狀況被控制後先停止阿托平，然後再停止巴姆。我們記錄人口統計學的資料、有機磷服食量、昏迷期間、呼吸器使用期間、住院期間、胸部 X 光發現、白血球記數、乙醯膽鹼酯酶濃度、血漿膽鹼酯酶濃度、阿托平使用總量、阿托平使用期間、巴姆使用總量、巴姆使用期間、尿液最高有機磷濃度、尿液有機磷出現期間和死亡案例，並且每八小時記錄尿液，用氣相層析法\火焰光度偵測法和氣相層析法\質譜法等檢測尿液有機磷，並紀錄尿液有機磷最高濃度。統計上使用 Wilcoxon rank sum test 來比較死亡及存活族群之各種項目，Fisher's exact test 被用來比較兩組胸部 X 光發現。結果為死亡組比存活組有較高的有機磷服食量、白血球記數和昏迷期間；有較低的住院期間、乙醯膽鹼酯酶濃度、血漿膽鹼酯酶濃度、巴姆使用總量和巴姆使用期間；但胸部 X 光發現、呼吸器使用期間、阿托平使用總量、阿托平使用期、尿液最高有機磷濃度和尿液有機磷出現濃度則無明顯的差別，死亡率為 20%。死亡組似乎沒有足量的巴姆治療，雖然死亡組及存活組巴姆使用期間的中位數比尿液有機磷出現期間的中位數高，但是巴姆使用期間的最大值小於尿液有機磷出現期間的最大值。長期的昏迷、低的乙醯膽鹼酯酶濃度及血漿膽鹼酯酶濃度和病人的臨床惡化結果有顯著之關係。

關鍵詞： 乙醯膽鹼酯酶，死亡率，有機磷，血漿膽鹼酯酶，預後

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