# Organophosphate Poisoning: 10 Years of Experience in Southern Taiwan

*Jong-Rung Tsai,[1] Chau-Chyun Sheu,[1] Meng-Hsuan Cheng,[1] Jen-Yu Hung,[1] Chuan-Sheng Wang,[2] Inn-Wen Chong,[1,3] Ming-Shyang Huang,[1,3] and Jhi-Jhu Hwang[1,3]*

[1]Department of Internal Medicine, Kaohsiung Medical University Hospital, [2]Department of Internal Medicine, Kaohsiung Municipal Hsiao-Kang Hospital, and [3]Department of Internal Medicine, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan.

Poisoning due to organophosphate pesticides is an important cause of morbidity and mortality worldwide. Although standard treatments involving the administration of atropine and oximes have been used, there remain many controversial areas concerning organophosphate poisoning (OPP). Herein, we present our 10 years of experience in assessing the severity of OPP in southern Taiwan. A retrospective study was performed on patients admitted with OPP. A total of 75 patients (50 males and 25 females) were studied between January 1996 and December 2005. Diagnosis was based on a clinical assessment and serum acetylcholinesterase (AChE) level at the time of hospital admission. The severity of OPP was assessed using the grading system of Bardin et al. The duration and dosage of atropine and palidroxime were recorded. All the biochemical data were analyzed. Sixty-one of the patients had attempted suicide and 14 patients had accidental exposure. The overall mortality rate was 8%. Muscarinic effects were observed in 66 (88%) of the OPP patients and the most frequent symptom was bronchial hypersecretion (52%). Among these three different severity groups, prolonged length of stay, higher infection rates, and higher mortality were found in the life-threatened group. The initial serum C-reactive protein (CRP) level was strongly correlated to the severity grading of the OPP. Nearly half of the patients were admitted to the intensive care unit (ICU) and, of this, 21 patients developed respiratory failure within 72 hours. Low serum AChE levels support the diagnosis of OPP, but no significant association was found between the severity of OPP and serum AChE levels. The grading system of Bardin et al is very helpful for physicians to facilitate the recognition of seriously poisoned subjects, and to permit their early admission to an ICU. Initial serum CRP, an acute phase reactant, had significant value in assessing the severity of the OPP. Although the management of acute OPP is supportive and the recovery rate is high, anti-cholinergic therapy should be used as soon as possible to counteract muscarinic effects. Physicians must be aware of the potential dangers of respiratory failure, which could occur within 72 hours of OPP.

**Key Words:** acetylcholinesterase, C-reactive protein, organophosphate poisoning
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Organophosphates (OPs), discovered more than 100 years ago, are the predominant group of insecticides used for pest control. Today, OPs are used worldwide in agriculture as well as in most household gardens. This ease of availability of the compounds has resulted in a gradual increase in accidental and suicidal poisoning, mainly in developing countries. OP pesticides inhibit acetylcholinesterase (AChE) at the muscarinic and nicotinic synapses by depositing a phosphoryl group at the enzyme's active site. This results in an accumulation of acetylcholine and uncontrolled activation of cholinergic synapses. Acute organophosphate

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Address correspondence and reprint requests to: Dr Jhi-Jhu Hwang, Department of Internal Medicine, Kaohsiung Medical University, 100 Shih-Chuan 1st Road, Kaohsiung 807, Taiwan.
E-mail: jhjhhw@cc.kmu.edu.tw

poisoning (OPP) causes tens of thousands of deaths each year across the world. The mortality rate of acute OPP is 10–20% [1–3] and the World Health Organization (WHO) has estimated that 200,000 people die each year from pesticide poisoning.

Signs of OPP are classified into effects secondary to muscarinic, nicotinic, and central nervous system (CNS) receptors being over-stimulated by the accumulation of acetylcholine at the synapses. A decrease in plasma AChE is usually used as confirmation of OPP, but the correlation between the enzyme level and the severity of clinical symptoms is poor. Atropine and oximes are the main treatment drugs. Atropine is used to counteract muscarinic effects such as bronchial hypersecretion, lacrimation, and bradycardia, but there is still much controversy about the therapeutic effect of oximes.

In this article, we report our 10 years of experience in the management of OPP. Although several scoring systems have been developed to help physicians identify life-threatened patients earlier, C-reactive protein (CRP), an acute phase reactant, can be an alternative severity index of acute OPP in addition to the scoring system of Bardin et al [4,5].

## Materials and Methods

Consecutive patients with acute OPP, who were admitted to Kaohsiung Medical University Hospital between January 1995 and December 2005, were enrolled in this study. A detailed history was taken from each patient. Exclusion criteria included carbamate poisoning or severe pre-existing chronic health status. Age, gender, chronic health status, type of OP ingested, initial and subsequent serum AChE levels, clinical presentation of OPP, dosage and duration of atropine, palidroxime (PAM), and outcomes were retrospectively analyzed by reviewing the medical records.

The diagnoses of acute OPP were based on the following criteria: (1) history of exposure to, or contact with, insecticides; (2) characteristic clinical signs and symptoms of OPP; (3) improvement of signs and symptoms after treatment with atropine or oximes; and (4) decreased serum AChE activity (OPP was considered if the lowest serum AChE activity was <50% of the laboratory minimum normal value) [1,6].

All patients received standard treatment for OPP, including gastric lavage and activated charcoal via nasogastric tubes. The patient's body was cleaned with soap and water immediately. Patients also received intravenous infusions of atropine to counteract muscarinic effects, such as bronchial hypersecretion, lacrimation, and bradycardia. Atropine can be used as an intermittent bolus infusion (1–2 mg per 2 hours) or continuous infusion (0.5–2 mg/hour). The goal of atropine infusion was to keep the heart rate around 80–120 bpm with clear breathing sounds. PAM was prescribed to patients who had OPP within 2 days. We followed WHO recommendations for PAM therapy (at least 30 mg/kg bolus followed by >8 mg/kg/hour infusion). Prior to treatment, blood samples were collected for blood count, serum electrolytes, and biochemistry analysis.

We graded patients with OPP according to the grading system developed by Bardin et al [4,5]. Their grading system groups OPP as mild, severe, or life-threatening. Mild OPP is determined by a history of exposure/intake with mild signs such as normal consciousness, mild secretions, and little fasciculation. Severe OPP is determined by a history of exposure/intake with severe signs including altered consciousness, copious secretions, and generalized fasciculation. Life-threatening OPP is defined by a history of exposure/intake with suicide attempt, stupor, $PaO_2$ < 75 mmHg, and abnormal chest roentgenogram. This grading system may not be applicable less than 8 hours after poisoning. At least two criteria are required to grade. If fewer criteria are present, then the previous grade is used.

Serum AChE activity was measured by colorimetric assays. The normal limits for serum AChE activity in our laboratory ranged from 5,100 to 15,500 U/L.

### *Statistical analysis*

Data were analyzed using JMP version 5.01 (SAS Institute Inc., Cary, NC, USA) and presented as mean ± standard deviation. The $\chi^2$ test was used for statistical analysis. One-way analysis of variance (ANOVA) was applied to assess differences among the groups. For the non-normal distribution data, Wilcoxon/Kruskal–Wallis test was used. Values of $p < 0.05$ were considered statistically significant.

## Results

During the study period, 75 patients with OPP were admitted to Kaohsiung Medical University Hospital.

**Table 1.** Clinical features of 75 patients with organophosphate poisoning*

| Characteristics | |
|---|---|
| Age (yr) | 45.0 ± 17.2 (range, 6–79) |
| Gender, male/female | 50/25 |
| Attempted suicide | 61 (81.3) |
| Atropine | |
| Dosage | 27.0 ± 38.4 mg |
| Duration of use | 6 ± 4.6 d |
| PAM | |
| Dosage | 16.4 ± 12.4 g |
| Duration of use | 5.5 ± 4.9 d |
| Mechanical ventilation | 21 (28) |
| ICU admission | 32 (42.7) |
| Mortality | 6 (8) |
| Muscarinic signs/symptoms | 66 (88) |
| Miosis | 34 (45) |
| Bronchial hypersecretion | 39 (52) |
| Diarrhea | 18 (24) |
| Salivation | 31 (41) |
| Bradycardia | 23 (31) |
| Nicotinic signs/symptoms | 35 (47) |
| Muscle fasciculations | 5 (7) |
| Tachycardia | 35 (47) |
| CNS signs/symptoms | 32 (43) |
| Seizure | 10 (13) |
| Unconsciousness | 12 (16) |
| Confusion | 20 (27) |

*Data are expressed as mean ± standard deviation or *n* (%). PAM = palidroxime; ICU = intensive care unit; CNS = central nervous system.

There were 25 female and 50 male patients. Their clinical characteristics are summarized in Table 1.

Nearly all the patients were poisoned through the gastrointestinal route, but three patients were poisoned through the inhalational route. No patient was poisoned intravenously. More than 10 different kinds of OP compounds were identified. The initial clinical presentations of the patients are shown in Table 1. Almost all the OPP patients had muscarinic symptoms and signs (66/75). The most frequent clinical signs were bronchial hypersecretion (52%), tachycardia (47%), miosis (45%), salivation (41%), and bradycardia (31%). When we compared patients who had CNS disorders with those without, we found that serum AChE levels (983.4 ± 195.8 U/L *vs*. 1,634.7 ± 168.9 U/L, $p = 0.014$) and length of stay (14.9 ± 1.6 days *vs*. 6.07 ± 1.4 days, $p = 0.002$) were significantly different between the two groups.

According to the grading system of Bardin et al [4,5], the 75 patients were divided into three groups (mild, severe, life-threatening OPP). In these three groups, serum AChE levels did not correlate to OPP severity ($p = 0.14$). The life-threatening OPP group had longer length of stay ($p = 0.002$), higher mortality ($p = 0.013$), and a higher infection rate ($p = 0.0006$). The mild OPP group had a lower incidence of intensive care unit (ICU) admission and respiratory failure. The age of OPP patients seemed to correlate to the severity of this grading system ($p = 0.04$). All of the above results are summarized in Table 2.

Initial serum CRP levels were taken from 40 patients when they arrived in our emergency room. The normal range of CRP in our hospital is ≤ 6 mg/dL. We found that initial serum AChE levels did not correlate to serum CRP levels. The serum CRP levels of the three groups (mild, severe, life-threatening OPP) are shown in Table 3. The serum CRP level increased in parallel to the severity grade of acute OPP ($p < 0.001$). Comparing the length of stay between the two groups (CRP ≤ 6 mg/dL *vs*. CRP > 6 mg/dL), the length of stay was significantly longer in the high CRP group (5.8 ± 4.2 days *vs*. 16.2 ± 2.1 days, $p = 0.03$).

The mean total dose of atropine given was 27.0 ± 38.4 mg (range, 0–260 mg) and the duration of atropine usage was 6 ± 4.7 days (range, 1–20 days). Thirty-three patients did not receive atropine because symptoms of muscarinic effects were not obvious in the initial presentations. Concerning the use of atropine among the different severity groups, the ratio of atropine use increased as the grade became more severe ($p = 0.003$) (Table 2). PAM was prescribed to 56 patients within 48 hours of poisoning. The average duration of PAM was 5.5 ± 4.9 days and the mean total dose was 16.4 ± 12.4 g. Prolonged PAM usage can increase serum AChE levels, but the amplitude of the serum AChE increase did not correlate with the duration of PAM use. There was no significant difference in overall mortality between patients with and without PAM usage (8.9% *vs*. 5.3%, $p = 0.6$). Among the three different OPP severity groups, there was no significant improvement of mortality in the life-threatening OPP group with PAM use (5/31) or without PAM use (1/7) ($p = 0.9$). PAM use also did not shorten the length of stay among these different OPP severity groups. For the respiratory failure patients, mortality did not improve either with PAM

**Table 2.** Grade of organophosphate poisoning severity in 75 patients

| | Mild ($n=33$) | Severe ($n=4$) | Life-threatening ($n=38$) | $p$ |
|---|---|---|---|---|
| Age (yr)* | 39.4 ± 2.9 | 48.0 ± 8.4 | 49.6 ± 2.7 | 0.04† |
| LOS (d)* | 5.9 ± 1.7 | 11.0 ± 4.7 | 13.9 ± 1.6 | 0.002† |
| AChE (U/L)* | 1,656.9 ± 195.8 | 1,016.6 ± 562.3 | 1,146.6 ± 182.4 | 0.34‡ |
| Median (25%, 75%) | 2,034 (261.5, 2,695) | 557.5 (184, 2,367.3) | 674.5 (206.2, 1,854.5) | |
| Mortality | 0% | 0% | 15.8% | 0.013§ |
| ICU admission days* | 0.6 ± 1.0 | 5.8 ± 2.8 | 5.6 ± 0.9 | 0.001† |
| Infection rate | 21.2% | 50% | 63.1% | 0.001§ |
| Mechanical ventilator | 9.1% | 50% | 44.7% | 0.001§ |
| Atropine use | 18.1% | 50% | 89.5% | 0.003§ |
| PAM use | 63.6% | 100% | 81.6% | 0.07§ |

*Data expressed as mean ± standard deviation; †analysis by ANOVA; ‡analysis by Wilcoxon/Kruskal–Wallis test; §analysis by $\chi^2$ test.
LOS = length of stay; AChE = acetylcholinesterase; ICU = intensive care unit; PAM = palidroxime.

**Table 3.** Relationship between C-reactive protein (CRP) and organophosphate poisoning severity

| | Mild ($n=16$) | Severe ($n=4$) | Life-threatening ($n=20$) | $p$† |
|---|---|---|---|---|
| CRP level (mg/dL)* | 15.2 ± 15.8 | 60.3 ± 27.3 | 82.9 ± 10.9 | 0.004 |
| Median (25%, 75%) | 10.1 (4.8, 31) | 62 (47.8, 71) | 70 (38.7, 110.5) | |

*Data expressed as mean ± standard deviation; †analysis by Wilcoxon/Kruskal–Wallis test.

use (28%) or without PAM use (33%) ($p=0.84$). However, days spent on ventilator support were decreased in patients treated with PAM (6.7 ± 1.9 days) compared to those who were not (23.0 ± 4.8 days) ($p=0.004$). There was no significant difference in PAM use among the three different OPP severity groups (Table 2).

Thirty-two patients were admitted to the ICU, with mean ICU admission of 3.5 ± 6.1 days. The serum AChE levels of ICU patients were lower than those of non-ICU patients (1,226.6 ± 200.4 U/L *vs.* 1,459.2 ± 77.6 U/L, $p=0.38$). Endotracheal intubation and ventilatory support were required in 21 patients, and all occurred within 72 hours. Comparison of serum AChE levels in mechanically ventilated and non-mechanically ventilated patients revealed significant difference (916.6 ± 238.4 U/L *vs.* 1,539.3 ± 153.6 U/L, $p=0.03$). Two patients became ventilator-dependent due to severe subsequent nosocomial infection. Three patients died within 48 hours of ICU admission. The causes of death were hepatic failure and acute renal failure, and their serum AChE levels were quite variable: 427.7, 50.4, and 1,092 U/L.

Biochemical analysis found hypokalemia in 10 patients (13.3%). Abnormal liver function was found in nine patients (12%). Five patients had aspiration pneumonia based on chest radiographs taken on the day of admission. Eight patients had Q-Tc prolongation on electrocardiography (ECG). Normal anion-gap metabolic acidosis was the prominent finding for the initial blood gas analysis, and respiratory alkalosis was the secondary finding.

## Discussion

OP compounds are used worldwide in agriculture as well as in household gardens. Ingestion of OP in an attempt to commit suicide is a major problem, especially in developing countries, because the sale of these items is over-the-counter in these countries. This ease of availability of the compounds has resulted in a gradual increase in accidental and suicidal poisoning. In our study, the rate of suicidal poisoning was 88%, probably because of the uncontrolled sale and use of these agents. It is also important to encourage farmers to use protective masks during spraying of OP to avoid accidental inhalation poisoning.

The inhibition of AChE activity leads to the accumulation of acetylcholine at the synapses, causing over-stimulation of muscarinic and nicotinic receptors.

The onset, intensity, and duration of OPP are determined largely by the nature of the particular compound and whether it exhibits reversible or irreversible AChE binding. Muscarinic manifestations include excessive salivation, miosis, diarrhea, and bradycardia. Nicotinic manifestations include muscle fasciculation and tachycardia. OP can also influence the CNS and result in seizures and altered consciousness. In this study, the most frequent signs were bronchial hypersecretion (52%), tachycardia (47%), miosis (45%), salivation (41%), and bradycardia (31%) (Table 1). Patients in this study with CNS disorders had lower serum AChE levels and longer length of stay than those without CNS disorders. So, CNS involvement is a poor prognostic factor for OPP patients and is consistent with the conclusions made by Bardin and van Eeden [4]. In addition, to stimulate the muscarinic and nicotinic receptors of the CNS, there may need to be higher acetylcholine levels by inhibition of AChE activity with OPP than the peripheral receptors. However, retrospective analysis limited our results about the exact onset, intensity and duration of clinical OPP symptoms and signs.

Namba et al described a grading method for patients with acute OPP based on clinical signs and symptoms, as well as on the degree of inhibition of serum AChE [7]. However, this proposed grading system has proven to be unworkable in clinical practice because serum AChE levels measured at the time of admission do not correlate with the clinical severity of poisoning [2,5,8,9]. Bardin et al [4,5] concluded that clinical respiratory and CNS symptoms and signs are the most important prognostic factors. They graded patients into mild, severe, and life-threatening OPP groups, and applied it to patients admitted to the ICU. The life-threatening OPP group had unfavorable outcomes even at lesser grades of severity. We adopted this grading system to organize our OPP patients.

Among the three groups, the serum AChE level of each group did not correlate to OPP severity. All cases of mortality occurred in the life-threatening OPP group. The life-threatening OPP group had longer length of stay ($p=0.002$), and higher mortality ($p=0.013$) and higher infection rates ($p=0.0006$). Only four patients were in the severe OPP group and this may be because of the small sample size or disadvantages of classification criteria. However, the value of this grading system can help the physician to recognize subjects with serious OPP early, and permit their admission to an ICU.

Several other grading systems have also been evaluated. The APACHE II, III and SAPS II clinical scoring tools seem to predict the severity of OPP, and may have prognostic value [2,10,11]. Using continuous, online, real-time spectral analysis of blood pressure and heart rate signals can also be a sensitive alternate index for earlier prediction of mortality in patients with acute respiratory problems induced by acute OPP [12].

CRP, first described in 1930, is an acute phase reactant and a marker of sepsis. In addition to infection, there are several other conditions that commonly lead to substantial changes in CRP concentrations. These include trauma, surgery, burns, tissue necrosis, immunologically mediated inflammatory disease, and advanced cancer [13,14]. In this study, initial serum CRP levels were strongly correlated to the severity grading of acute OPP (Table 3), but had no relationship to serum AChE levels. Patients in higher serum CRP level groups also had longer length of stay. In addition to other grading systems, CRP can be a good alternative index to evaluate the severity of acute OPP. However, this was a retrospective analysis and we did not have the data on serial serum CRP levels during or following the management of the acute OPP patients. A prospective study to confirm the value of CRP may be needed.

Oximes reactivate AChE by removing the phosphoryl group. PAM is the oxime most often used worldwide. The main therapeutic effect of PAM is the recovery of neuromuscular transmission at the nicotinic synapses. *In vitro* experiments have shown that oximes are effective in reactivating human AChE inhibited by OP compounds [15]. The clinical usefulness of oximes has been challenged over the past 20 years in many parts of the world as many have failed to see benefits in their practice [16]. Current evidence is insufficient for determining whether oximes are harmful or beneficial in the management of acute OP pesticide poisoning [17]. Peter et al also suggest that oximes are associated with either a null effect or possible harm [18].

In our study, serum AChE level was increased by prolonged PAM usage, but the increase did not have a significant correlation to the duration of PAM usage. Among the three different OPP severity groups, both the mortality and length of stay did not improve with PAM usage. For OPP patients with respiratory failure, PAM usage did not improve mortality, but it did shorten the number of days spent on ventilator

support. Although serum AChE levels did increase with PAM usage, the mortality rates were not significantly decreased by PAM usage. PAM can improve ventilator weaning for OPP patients with respiratory failure. However, the small sample size may render the above results less significant.

Between the ICU and non-ICU patient groups, lower serum AChE levels were found in the ICU group. This result may come from the incorrect belief that lower serum AChE levels indicate a higher severity of acute OPP. The emergency room physicians may then have arranged for intensive care for these patients. Acute OPP-induced respiratory failure usually develops within 24 hours. In some case, it develops 24–96 hours after poisoning [3]. In this report, all the patients developed respiratory failure within 72 hours after poisoning, and most of them developed it within 24 hours. The initial serum AChE of the respiratory failure group was significantly different from that of the non-respiratory failure group. Only two patients became ventilator-dependent and the causes of ventilator-dependence were severe subsequent nosocomial infection and underlying disease. Although the need for assisted ventilation is usually considered as an indicator of illness severity in patients with acute OPP [3], the mainstays of respiratory failure treatment is supportive and to control the subsequent infection.

In our report, the ratio of OPP patients without atropine use was high because there were no obvious muscarinic effects in these patients. The high ratio may be the result of either of the following two reasons: (1) although some OPP patients did not present with significant poisoning, they were still admitted for observation and treatment because the exact onset and intensity of clinical OPP symptoms, signs, and comorbidities were unclear; (2) the ratio of muscarinic effects of OPP, such as hypersecretion and bradycardia, were not high, which seem comparable to the atropine use ratio. The atropine use ratio (27/32) on ICU admission of OPP patients was the same as in other reports [2]. As OPP severity worsened, atropine use also increased (Table 2). However, we included less severe OPP patients in this study and this may have influenced our results and mortality rate.

Mortality rates of acute OPP range from 10% to 20% and the causes of death were central respiratory failure or the direct toxic effects of OPP [1,3]. The usual causes of early death were chiefly related to CNS depression [19], ventricular arrhythmias [20], or respiratory failure [3]. Our mortality rate (8%) was lower than other reports. Three patients developed multiple organ failure within 2 days. The main causes of mortality in these three patients were hepatic failure and renal failure, which are unusual. The other patients died of subsequent severe nosocomial infection.

In conclusion, low serum AChE levels support the diagnosis of OPP, but no significant association is present between the severity of poisoning and serum AChE levels. The grading system of Bardin et al [4,5], is very helpful for physicians to facilitate the recognition of seriously poisoned subjects and to permit their early admission to an ICU. Initial serum CRP levels can be an excellent indicator of the severity of acute OPP, but its role in following acute OPP is not clear. Although the main management of acute OPP is supportive and our recovery rate was above 90%, atropine should be used as soon as possible to counteract the muscarinic effects. PAM use still needs more evidence to confirm its role in the management of OPP. Physicians must be aware of the potential dangers of respiratory failure, which could occur within 72 hours of OPP.

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# 南台灣十年之有機磷中毒病例分析

蔡忠榮[1]　許超群[1]　鄭孟軒[1]　洪仁宇[1]　王傳生[2]
鍾飲文[1,3]　黃明賢[1,3]　黃吉志[1,3]
[1]高雄醫學大學附設醫院　胸腔內科
[2]高雄市立小港醫院　內科
[3]高雄醫學大學　醫學院醫學系　內科學

有機磷中毒是全世界重要的死因之一，oximes 及阿托品是治療有機磷中毒的主要藥物，但是對於有機磷中毒治療方面仍有許多爭議。本篇文章主要針對西元 1996 年到 2005 年，本院有機磷中毒患者做回溯性探討，提供有關有機磷中毒治療的經驗及找出其他重要的有機磷中毒的臨床評估指標。此研究共有七十五位有機磷中毒患者，包含 50 個男性及 25 個女性患者，死亡率約 8%。61 個患者是因自殺而導致有機磷中毒，其他則是意外中毒。其中 88% 的患者出現蕈毒作用，尤其以呼吸道分泌物增加為主要症狀。依據病患臨床嚴重度分成三組：在致命性這組發現有較高的住院天數、感染率及死亡率。起始的血清 C 反應性蛋白濃度高低和有機磷中毒嚴重程度呈現高度的相關性。約一半的有機磷中毒患者需要加護病房的照顧，21 個患者出現呼吸衰竭現象。有機磷中毒會引起血清中的乙醯膽鹼酯酶濃度下降，但是血清中的乙醯膽鹼酯酶濃度下降的程度則和臨床嚴重程度並無相關性。Bardin 等人提出有機磷中毒的分級方法可提供臨床醫師早期去評估患者及針對致命性的有機磷中毒患者安排加護病房照護。起始的血清 C 反應性蛋白濃度則提供另一種臨床嚴重度的評估。雖然有機磷中毒的處理主要是以支持性療法及抗乙醯膽鹼作用為主，但是在中毒後的 72 小時內臨床醫師必須特別注意呼吸衰竭發生的可能性。

**關鍵詞**：乙醯膽鹼酯酶，C 反應性蛋白，有機磷中毒
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通訊作者：黃吉志醫師
高雄醫學大學附設醫院胸腔內科
高雄市807三民區自由一路100號