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Respiratory Failure of Acute Organophosphate and Carbamate Poisoning*

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Respiratory failure (RF) developed in 43 (40.2 percent) of 107 patients with acute organophosphate or carbamate poisoning; 22 (51.2 percent) died. The 64 patients who did not develop RF survived. All cases of RF developed within 96 hours after poisoning: within 24 hours in 35 patients (acute onset) and between 24 and 96 hours in eight patients (subacute onset). Severity of poisoning was the primary determinating factor for RF. Cardiovascular collapse and pneumonia were also associated with RF. In 19 patients with cardiovascular collapse, 17 had acute onset of RF and two had subacute onset. In 28 patients with pneumonia, 17 developed acute onset of RF and eight developed subacute onset. No organophosphorus compound caused RF more frequently than another. The duration of ventilator support for subacute RF was significantly longer than for acute RF (287 ± 186 vs 115 ± 103 hours, p = 0.02). The use of pralidoxime did not reduce the incidence of RF. We found that severity of poisoning, cardiovascular collapse, and pneumonia were the predisposing factors to RF. The golden time for treatment of acute organophosphate or carbamate poisoning was the initial 96 hours. No RF occurred after this time. Aggressive treatment and prevention of the above three factors will reduce the incidence of RF, or in other words, reduce the mortality. ***(Chest 1990; 98:631-36)***

RF = respiratory failure

Because of the widespread use and availability of agricultural insecticides,[1,2] suicidal or inadvertent poisoning became a common and serious problem in Taiwan. The mortality of organophosphate varied from 10 to 86 percent,[3,4] staying from 10 to 20 percent during the past ten years with intensive care management, such as large-dose atropine and pralidoxime therapy, as well as ventilator support for respiratory failure (RF).[5,6] The cause of death was thought to be a combination of excessive bronchial secretions, pulmonary edema, bronchospasm, respiratory muscle paralysis, and paralysis of the respiratory medulla, summarily, "RF."[5-7] This study consists of 107 patients with acute organophosphate or carbamate poisoning whose RF was analyzed according to different onset times. Associated disorders, such as cardiovascular collapse and pneumonia, are discussed.

Materials and Methods

One hundred seven patients were admitted to Chang Gung Memorial Hospital with the diagnosis of acute organophosphate or carbamate poisoning during the period 1982 to 1987. All patients received first aid and further treatment at this medical center; referred patients were excluded from this study to avoid the confusion in data analysis. The diagnosis of acute organophosphate or carbamate poisoning was based on the following: (1) a history of short-term exposure or contact; (2) the characteristic clinical signs and symptoms; (3) improvement of those signs and symptoms after treatment with atropine and pralidoxime; and (4) decrease in the cholinesterase activity in the serum.[6,7] Normal values for the serum cholinesterase activity in this hospital's laboratory were 3,000 to 6,000 mU/ml. According to the classification of severity, poisoning was defined as severe when the lowest serum cholinesterase activity was less than 300 mU/ml, as moderately severe from 300 to 600 mU/ml, as mild from 600 to 1,500 mU/ml, and as very mild from 1,500 to 3,000 mU/dl.[1,8]

Respiratory failure was diagnosed as respiratory distress, hypoventilation, and arterial blood gas with a PaO_2 of less than 50 to 60 mm Hg and a $PaCO_2$ of greater than 50 to 55 mm Hg accompanied by acidemia (pH<7.30).[9] Cardiovascular collapse (without effective cardiac output) was defined clinically as when peripheral pulsation could not be palpated and blood pressure could not be detected by phlebomanometer, even if there was a heart rhythm on the ECG monitor. The criteria for pneumonia were that there were new pulmonary infiltrates not explained by any other means and with at least two of the following: (1) raised white blood cell count; (2) purulent bronchial secretions; and (3) positive Gram stain and culture of sputum.[2]

For treatment, large, repeated doses of atropine were given intravenously on arrival to the emergency room until signs of atropinization (mydriasis, pupil size <3 mm; tachycardia, heart rate >100 beats/min; flushing; xerostomia; anhydrosis; etc) appeared. Then a maintenance dose was given to keep patients atropinized until the signs and symptoms of poisoning resolved completely.[1,2,7,9-11] The pralidoxime was given intravenously in most patients within the first 36 hours.[1,2,7,9,12,13] Endotracheal intubation and ventilator support were given immediately whenever RF was diagnosed.

To compare the means of three or more independent groups, we used the one-way analysis of variance (ANOVA) test. To evaluate the differences in the qualitative variables, we used the χ^2 test. Student's t test was used to evaluate the differences between the two groups' quantitative variables. A regression models (including Pearson

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Table 1—*Route of Poisoning and Its Relationship with Severity and Outcome in Acute Organophosphate and Carbamate Poisoning*

Route	Total (%)	Severity*				Outcome	
		Sev (%)	Mod (%)	Mild (%)	V Mild (%)	Died (%)	Alive (%)
Attempted suicide	70 (65)	37 (53)	5 (7)	10 (14)	18 (26)	18 (26)	52 (74)
Poisoning during farming†	20 (19)	3 (15)	5 (25)	7 (35)	5 (25)	1 (5)	19 (95)
Poisoning during manufacture†	1 (1)	1				0	1
Accidental ingestion	10 (9)	5 (50)	2 (20)	0	3 (30)	2 (20)	8 (80)
Unknown	6 (6)	3 (50)	2 (33)	1 (17)	0	1 (17)	5 (83)
Total	107	49 (46)	14 (13)	18 (17)	26 (24)	22 (21)	85 (79)

*Severity: serum cholinesterase activity: sev = severe <300; mod = moderate, 300 to 600; mild = 600 to 1,500; v mild = very mild, 1,500 to 3,000 mU/ml of serum.

†Poisoning during farming and manufacture resulting from skin contact and/or inhalation.

correlation coefficients) for dependent variable—RF—was used to examine the predictor variables of gender, age, severity, pneumonia, and cardiovascular collapse.

Results

Included in this study are 107 patients from 1982 to 1987: 60 were male and 47 were female. The mean age (± SD) was 41.5 ± 19.3 years (range, 2 to 85 years). Eighty of them had acute organophosphate poisoning, 13 had acute carbamate poisoning, and 14 had either both or an uncertain agent. The source of poisoning is shown in Table 1. Attempted suicide, the most common, had the highest severity and mortality.

Respiratory failure developed in 43 patients (40.2 percent of the total). Thirty-five patients had acute onset, occurring during the first 24 hours after poisoning, with a mortality rate of 57.1 percent (20/35). In eight patients, RF occurred between 24 and 96 hours after poisoning, subacute onset, with a mortality rate of 25 percent (2/8). No RF developed after 96 hours. There was no mortality in patients without RF. The overall mortality rate was 20.6 percent (22/107). Seven patients died within 24 hours (acute stage), 11 patients from 24 to 96 hours (subacute stage). The remaining died between four and 22 days after poisoning of septic shock (one), barotraumatic pneumothorax (one), and profound pneumonia with RF (two). All patients with acute carbamate poisoning survived, although two of them developed RF.

Table 2 summarizes the number of patients by different degree of severity and their relationship with RF. The patients with RF had more severe poisoning.

Cardiovascular collapse occurred on arrival in 19 patients (17.8 percent); 17 developed acute RF, and two developed subacute RF. Pneumonia developed in 28 patients (26.2 percent); 19 had acute onset during the first 24 hours after poisoning, and nine had subacute onset between 4 and 96 hours after poisoning. The relationship between pneumonia and RF is summarized in Table 3. Most patients with pneumonia developed RF.

Signs and symptoms were not completely recorded in all cases in this retrospective study. Table 4 illustrates only the positive numbers and their distribution in different degrees of severity. Although there was no correlation between severity and incidence of signs and symptoms, the patients with higher severity had significantly higher mortality (Table 4). There were 14 kinds of organophosphate compound contributing to the poisoning in our patients; merinphos and parathion were the most common. No special organophosphate compound resulted in RF or fatal outcome more frequently than others.

The mean (± SD) dosage of atropine therapy in the first 24 hours was 37 ± 56 mg (range, 1 to 437 mg). The varieties of dosage in different severities of poisoning and RF status are shown in Figure 1. Both severity and RF status influenced the dosage of atropinization. Twelve patients had at least one episode of atropine psychosis.

Because pralidoxime was not a standard medication for the treatment of acute organophosphate or carbamate poisoning in our hospital, it was only administered to 82 patients: 68 of the 80 patients with organophosphate poisoning, five of the 13 patients

Table 2—*Relationship between Respiratory Failure and Severity in Acute Organophosphate and Carbamate Poisoning**

	Total (%)	Severe (%)	Moderate (%)	Mild (%)	Very Mild (%)
Acute RF	35 (33)	28 (80)	3 (8)	2 (6)	2 (6)
Subacute RF	8 (7)	7 (88)	1 (12)	0	0
Without RF	64 (60)	14 (22)	10 (16)	16 (25)	24 (37)
Total	107	49 (46)	14 (13)	18 (17)	26 (24)

*RF = respiratory failure. Severity: serum cholinesterase activity: severe <300; moderate, 300 to 600; mild, 600 to 1,500; very mild, 1,500 to 3,000 mU/ml of serum.

Table 3—*Relationship between Respiratory Failure and Pneumonia in Acute Organophosphate and Carbamate Poisoning**

	Total (%)	Acute P (%)	Subacute P (%)	Without P (%)
Acute RF	35 (33)	15 (43)	3 (9)	17 (48)
Subacute RF	8 (7)	2 (25)	5 (63)	1 (12)
Without RF	64 (60)	2 (3)	1 (2)	61 (95)
Total	107	19 (18)	9 (8)	79 (74)

*P = pneumonia; RF = respiratory failure.

Table 4—*Distribution of Positive Clinical Signs, Symptoms, and Outcome by Severity in Acute Organophosphate and Carbamate Poisoning**

	Total	Sev (%)	Mod (%)	Mild (%)	V Mild (%)
Total	107	49 (46)	14 (13)	18 (17)	26 (24)
Sweating	21	6 (29)	6 (29)	3 (14)	6 (28)
Salivation	42	22 (52)	6 (14)	5 (12)	9 (22)
Nausea	47	19 (41)	7 (15)	10 (21)	11 (23)
Miosis	83	43 (52)	10 (12)	15 (18)	15 (18)
Disturbed consciousness	54	28 (52)	6 (11)	9 (17)	11 (20)
Apnea	16	11 (69)	2 (13)	2 (13)	1 (7)
Cardiovascular collapse	19	14 (74)	2 (11)	2 (11)	1 (6)
Outcome					
Alive	85	31 (37)	11 (13)	18 (21)	25 (29)†
Died	22	18 (82)	3 (14)	0 (0)	1 (4)

*Severity: serum cholinesterase activity: Sev = severe <300; Mod = moderate, 300 to 600; Mild = 600 to 1,500; V Mild = very mild, 1,500 to 3,000 mU/ml of serum.
†p = 0.001.

with carbamate poisoning, and nine of the 14 patients with both or an uncertain agent. The relationship between pralidoxime therapy and RF by degree of severity is summarized in Table 5. Pralidoxime could not prevent RF.

Ventilator support was given to all patients with RF. The duration of ventilator support was from six to 512 hours (mean, 158 ± 145) in 21 survivors of RF, and in nine of them it was more than seven days. In 15 survivors of acute RF, the mean (± SD) duration of ventilator support was 115 ± 103 hours (range, six to 295 hours). In six survivors of subacute RF, the mean (± SD) duration of ventilator support was 287 ± 186 hours (range, 72 to 512 hours). The duration of ventilator support for the subacute RF was significantly higher than it was for the acute RF (p = 0.02).

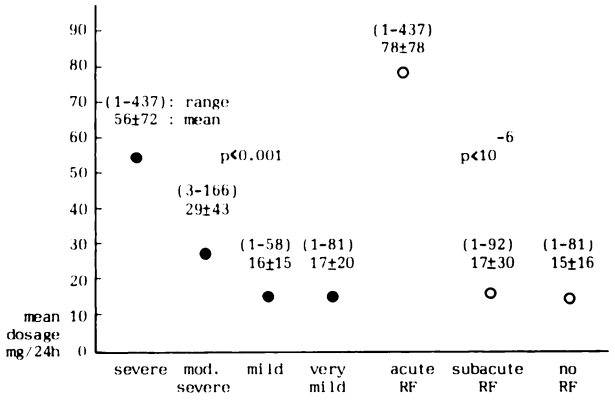

FIGURE 1. Mean dosage of atropine therapy in the first 24 hours by severity and respiratory failure (RF).

In these 21 survivors of RF, the mean (± SD) serum cholinesterase level was 384 ± 489 mU/ml at the time of RF and was 1,264 ± 1,313 mU/ml at the time of successful weaning from ventilator support (p = 0.01).

The severity of poisoning ($p<10^{-6}$), cardiovascular collapse ($p<10^{-8}$), and pneumonia ($p<10^{-8}$) were the predisposing factors to RF, but they were dependent on each other; the correlation analysis shows that any pair of them had statistical correlation (Table 6).

Discussion

Acute organophosphate poisoning was the most common type of poisoning in Taiwan. The major cause of poisoning in our study was attempted suicide (65.4 percent); this kind of patient always had more severe poisoning because the amount ingested was larger than the other types of exposure, such as accidental ingestion or skin contact. This accounts for the fact that nearly half our patients had more severe poisoning and a higher mortality rate (20.6 percent) than in other studies.[3,5,6]

The respiratory symptoms of the muscarinic effects, including rhinorrhea and bronchial secretion, bronchospasm, and laryngeal spasm, may develop, which can result in airway obstruction. The respiratory symptoms of the nicotinic effects are associated with paralysis of the respiratory muscles. Weakness of the muscles of the tongue and pharynx aggravate the upper airway obstruction. Finally, there may be a central depression of respiration leading to cessation of breathing.[14,15] This is thought to be a result of direct

Table 5—*Relationship between Pralidoxime Therapy and Respiratory Failure by Severity in Acute Organophosphate and Carbamate Poisoning**

		Total (%)	Sev (%)	Mod (%)	Mild (%)	V Mild (%)
With	Acute RF	33 (40)	26 (79)	3 (9)	2 (6)	2 (6)
PAM	Subacute RF	7 (9)	6 (86)	1 (14)	0	0
therapy	Without RF	42 (51)	10 (24)	6 (14)	10 (24)	16 (38)
	Total	82	42 (51)	10 (12)	12 (15)	18 (22)
Without	Acute RF	2	2 (100)	0	0	0
PAM	Subacute RF	1	1 (100)	0	0	0
therapy	Without RF	22	4 (18)	4 (18)	6 (27)	8 (36)
	Total	25	7 (28)	4 (16)	6 (24)	8 (32)

*RF = respiratory failure; PAM: pralidoxime. Severity: serum cholinesterase activity: Sev = severe <300; Mod = moderate, 300 to 600; Mild = 600 to 1,500; V Mild = very mild, 1,500 to 3,000 mU/ml.

action of the organophosphate at the cholinergic synapses in the brain stem that are involved in the control of respiration.[16,17] In man, the failure of the central respiratory drive seems to be the most important factor, and the peripheral neuromuscular block is a secondary factor for RF.[16,18,19] The initial respiratory symptoms as described above and final RF always developed during the period of cholinergic crisis, usually during the first 24 hours after exposure to organophosphate. But Wadia et al[20] and Senanayake et al[21] described intermediate neurotoxic effects, the paralysis of proximal limb muscles, neck flexors, motor cranial nerves, and respiratory muscles, occurring 24 to 96 hours after poisoning, after recovery from cholinergic crisis while still receiving atropine treatment. Most patients with these intermediate neurotoxic effects developed RF and more than half of the patients with RF died. Although the initial cholinergic phase responded well to atropine alone, the intermediate neurotoxic effects did not respond to atropine.[20,21]

Respiratory failure developed in 40.2 percent of our patients, an incidence similar to previous reports.[5,6] In nearly 80 percent of these cases, the RF developed during the first 24 hours after exposure; it may have occurred due to the muscarinic and nicotinic effects of the acute organophosphate poisoning. The mortality rate was particularly high (57.1 percent) in this group. Of the remaining eight patients whose RF developed between 24 and 96 hours after exposure, only two died. The mechanism of RF during this period of time (subacute) in our patients does not seem to be the same as described by Wadia et al[20] and Senayake and Karalliedde.[21] Seven of these eight patients had complications of pneumonia, and five were subacute. The timing of pneumonia was consistent with the onset of RF. In addition, in five of these eight patients, the lowest serum cholinesterase level appeared during the subacute period. The above two factors may account for the timing of the subacute RF.

Although there was no correlation between clinical signs, symptoms, and severity of poisoning, RF developed almost entirely in the groups with moderately severe and severe poisoning, except for two cases in the mild and another two in the very mild group. Cardiovascular collapse occurred in three patients and pneumonia in two of these four patients. Besides the above two predisposing factors for RF, two patients with cardiovascular collapse died on the first day after

Table 6—*Factors Predictive of Respiratory Failure in Acute Organophosphate Poisoning**

	Total	With RF (%)	Without RF (%)	p Value
Sex				
Male	60	27 (45)	33 (55)	
Female	47	16 (34)	31 (66)	=0.34
Age, yr				
≤50	36	15 (42)	21 (58)	
>50	71	28 (39)	43 (61)	=0.99
Severity				
Severe	49	35 (71)	14 (29)	
Moderate	14	4 (29)	10 (71)	
Mild	18	2 (11)	16 (89)	
Very mild	26	2 (8)	24 (92)	$<10^{-6}$
With pneumonia	28	25 (89)	3 (11)	
Without pneumonia	79	18 (23)	61 (77)	$<10^{-8}$
With CV collapse	19	19 (100)	0 (0)	
Without CV collapse	88	24 (27)	64 (73)	$<10^{-8}$

*Severity: serum cholinesterase activity: severe <300; moderate, 300 to 600; mild, 600 to 1,500; very mild, 1,500 to 3,000 mU/ml of serum. RF = respiratory failure; CV collapse = cardiovascular collapse.

poisoning, so the serum cholinesterase level might have not fallen to the lowest level and led to an underestimation of severity.

Cardiovascular collapse was found in 19 of our patients. This may result from depression of the circulatory center or a complication of profound hypoxemia, hypercapnia, and acidemia from RFs.[22] All of these 19 patients suffered from RF. Pneumonia developed in about a quarter of our patients, and in all of them it occurred within 96 hours. This time of onset can almost exclude the etiology of hospital-acquired infection. Because in acute organophosphate poisoning there is depressed consciousness and cough reflex, accompanied by large amount of respiratory secretions and emesis, as well as the gastric lavage used in the first aid, aspiration is most likely the main cause of pneumonia. The patients who had pneumonia, of course, had a higher risk for RF. Around 80 percent of the patients with pneumonia developed RF in our series; this finding was similar to 76 percent reported by Bardin et al.[6]

The dosage of atropine used for treatment in the first 24 hours was significantly different between patients with different degrees of severity of poisoning in our series. This finding suggested that the clinical signs of atropinization (mydriasis, pupils size <3 mm; tachycardia, heart rate >100/min; flushing; xerostomia; anhydrosis; etc) were rather reliable criteria for the judgment for dosage of atropine therapy.

Pralidoxime is a biochemical antidote for organophosphate poisoning; its beneficial effects include reactivation of cholinesterase by cleavage of phosphorylated active sites, direct reaction and detoxification of unbounded organophosphate molecules, and an endogenous anticholinergic effect.[9,12,13] Pralidoxime reversed the effects of cholinergic nicotinic stimulation that are unaffected by the use of atropine alone.[2,5,20] Pralidoxime was used in most of our patients but it did not seem to work to reduce the incidence of RF in organophosphate poisoning. Although pralidoxime treatment in carbamate poisoning is still equivocal, five of our 13 patients with carbamate poisoning treated with it had no adverse outcome.

The mean duration of ventilator support in survivors of RF in our series was equal to that reported by Du Toit et al[5] (6.6 ± 4.2 days). The duration of ventilator support was significantly longer for patients with subacute RF than it was for patients with acute RF. This may be explained by the fact that all six survivors of subacute RF also had pneumonia. Although Adams et al[23] stated that spontaneous recovery of central respiratory function after organophosphate poisoning may not be related to the return of cholinesterase activity, the serum cholinesterase activity on weaning had returned to three times what it had been at the start of ventilator support. Thus, as described by Du Toit et al[5] and Hassan et al,[24] the serum cholinesterase activity may be a guide to the treatment and prognosis of patients with organophosphate intoxication, although it had wide range of normal.

In conclusion, all the RF complications of acute organophosphate poisoning occurred during the first 96 hours after exposure. The presence of RF suggested a poor prognosis. We found that severity of poisoning, cardiovascular collapse, and pneumonia were the predisposing factors to RF. We suggest that more aggressive dosage in atropinization, immediate management of cardiovascular collapse, careful maintenance of airway patency, and painstaking attention to prevent aspiration pneumonia when performing gastric lavage for poisoning will reduce the incidence of RF, or in other words, reduce the mortality.

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