Research article

Intensive care management of organophosphate insecticide poisoning

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Abstract

Introduction Organophosphate (OP) insecticides inhibit both acetylcholinesterase and pseudocholinesterase activities. The clinical course of OP poisoning may be quite severe and may need intensive care management. We report our experience with the intensive care management of serious OP insecticide poisonings.

Methods A retrospective study was performed on the patients with OP poisoning followed at our medical intensive care unit. Forty-seven patients were included. Diagnosis was performed from the history taken either from the patient or from the patient's relatives regarding the agent involved in the exposure. Intravenous atropine and pralidoxime was administered as soon as possible. Pralidoxime could not be given to 16 patients: 2 patients did not receive pralidoxime because they were late admissions, and 14 did not receive pralidoxime because the Ministry of Health office was out of stock. Data are presented as mean ± standard deviation.

Results There were 25 female and 22 male patients. Thirty-two (68%) were suicide attempts and 15 (32%) were accidental exposure patients. The mortality rates for the patients who did and did not receive pralidoxime were 32 and 18.7%, respectively and were not statistically different. Ten patients (21.2%) required mechanical ventilation. The mortality rate for the patients who required mechanical ventilation was 50%, but the rate was 21.6% for those patients who were not mechanically ventilated. Intermediate syndrome was been observed in 9 (19.1%) patients. Complications were observed in 35 (74.4%) patients. The duration of the intensive care stay was 5.2 ± 3.0 days.

Conclusion OP insecticide poisoning is a serious condition that requires rapid diagnosis and treatment. Because respiratory failure is the major reason for mortality, careful monitoring, appropriate management and early recognition of this complication may decrease the mortality rate among these patients.

Keywords anticholinesterase, atropine, organophosphate pesticides, poisoning, pralidoxime

Introduction

Hundreds of organophosphate (OP) compounds are currently available to use as insecticides [1]. OP insecticides inhibit both cholinesterase and pseudocholinesterase activities [2], as they are irreversible cholinesterase inhibitors. The inhibition of cholinesterase activity leads to accumulation of acetylcholine at synapses, causing overstimulation and disruption of neurotransmission in both central and peripheral nervous systems [2]. Exaggerated manifestations of nicotinic and muscarinic receptors appear as a result of these actions [3]. OP insecticides are one of the most important causes of poisoning in Turkey, as in many developing countries [4]. The mode of exposure to OP insecticides varies, including dermal, gastrointestinal, inhalational

OP = organophosphate.

and intravenous routes [2,5,6]. Poisoning occurs as a result of agricultural use, accidental exposure, suicide and, rarely, homicide [2,7,8]. The mortality rate of OP poisoning is high: fatal issue is often related to a delay in diagnosis or an improper management. Early diagnosis and appropriate treatment, conversely, are often life saving, although the clinical course of OP poisonings might be quite severe and necessitate intensive care management. In this article, we report our experience with the intensive care management of serious OP insecticide poisonings.

Methods

A retrospective study was conducted on patients with OP poisoning admitted to our nine-bed medical intensive care unit between January 1990 and January 2000. Forty-seven patients were included. The diagnosis was based on information taken either from the patient or from the patient's family about the agent involved in the exposure. We could not confirm the diagnosis by measuring plasma or red blood cell anticholinesterase levels since these are not measured in our hospital. Toxlab screening of the patients was also not performed because it is not available at our institution. Treatment was implemented as soon as the diagnosis of OP insecticide poisoning was suspected. Atropine and/or pralidoxime sulfate was administered. Atropine is given either as a continuous infusion or intermittent dosing. Continuous infusion was started as 0.02–0.08 mg/kg per hour until control of hypersecretion occurred. Heart rates exceeding 130 beats/min were avoided using intravenous diltiazem or propranolol for myocardial protection. Intermittent dosing was performed using 2 mg atropine every 15 min until secretions were controlled. Heart rate and pupil size were not used as indices as long as the heart rate was above 60 beats/min. Atropine was discontinued 24 hours after all signs of atropinisation occurred and drying of secretions was achieved. Pralidoxime sulfate was administered as 4 g daily divided to four doses for every patient as long as available. We obtained pralidoxime from the offices of the Ministry of Health in Kayseri. Pralidoxime is prescribed to the patient's relatives and they receive it from these offices free of charge. Pralidoxime is unfortunately sometimes not available at these offices.

Blood gas and routine biochemistry were performed daily. Gastric lavage followed by administration of activated charcoal via nasogastric tube, and cleansing of the patient's body with soap and water was started. The patients were admitted to the intensive care unit based on the severity of the clinical signs and symptoms. The indications for endotracheal intubation and mechanical ventilation were as follows: excessive secretions; a depressed level of consciousness, which causes an inability to protect the airway; poor gas exchange, which was unresponsive to oxygen treatment; cardiorespiratory arrest; and severe metabolic acidosis with hemodynamic instability (systolic blood pressure <90 mmHg). Synchronized intermittent mandatory ventilation + pressure support mode in either pressure-controlled or volume-controlled form was started. The positive end expiratory pressure was initially applied as 5 cmH_2O and then titrated to keep SaO_2 above 94% with 40% FIO_2. Weaning from mechanical ventilation was carried out with pressure support weaning and T-tube trials. The chi-square test was used for statistical analysis. Data are presented as mean ± standard deviation.

Results

During the study period, 47 patients who had OP poisoning with a known agent were admitted to the medical intensive care unit. There were 25 female and 22 male patients. The mean age was 30 ± 15 years when admitted to the medical intensive care unit of a 600-bed university hospital. Thirty-two (68%) patients were suicide attempts and 15 (32%) were accidental exposure. Forty-four (93.6%) of the patients were poisoned through the gastrointestinal route. One (2.1%) patient had inhalational poisoning and two (4.2%) patients had intravenous injection for suicidal purposes. There were 10 different types of OP insecticide agents involved (Table 1). The estimated average time for the admission to the emergency department after the exposure was 9.4 hours (range, 1–96 hours). The most frequent clinical signs were meiosis, change in mental status, hypersalivation, agitation and fasciculations (Table 2).

All of the patients received atropine. Atropine was administered during 3.4 ± 2.1 days and the average total atropine dose was 79.1 ± 62.9 mg. A total of 31 (66%) patients received pralidoxime. Pralidoxime was given for 1.9 ± 1.4 days and the average dose was 3.5 ± 3.0 g. Pralidoxime was not administered to 16 (34%) patients. The mortality rate among patients treated with pralidoxime was 32.0% (10 patients), but the rate was 18.7% (3 patients) for patients not treated with pralidoxime ($P > 0.05$). Thirty-seven of the patients (78.7%) were exposed to OP with moderate toxicity ($LD_{50} > 500$ mg/kg), 9 patients (19.1%) to OP with high toxicity ($LD_{50} < 50$ mg/kg) and 1 patient to an agent with low toxicity ($LD_{50} > 1000$ mg/kg). Nine patients died in the moderate toxicity group and four patients died in the high toxicity group ($P > 0.05$). Mechanical ventilatory support was needed for 10 (21.2%) patients. Average arterial blood gas values of these patients were as follows: pH 7.26 (range, 6.93–7.45); pCO_2, 40.2 mmHg (range, 22–53 mmHg); pO_2, 68.2 mmHg (range, 50–91 mmHg); HCO_3, 14.2 mmol/l (range, 10–25 mmol/l); SaO_2, 87.5% (range, 78–95%). The duration of mechanical ventilation was 4.1 ± 3.2 days. The mortality rate for the patients who were mechanically ventilated was 50% (5 patients), although the mortality rate was 27.6% (13 patients) for all patients. The mortality rate for the mechanically ventilated patients was not statistically different compared with

those patients not mechanically ventilated. Two patients who are mechanically ventilated died with sudden cardiorespiratory arrest following ventricular tachycardia, and three died from pneumonia and complicating adult respiratory distress syndrome. Intermediate syndrome has been observed in 9 (19.1%) of the patients: 4 of these patients required mechanical ventilation, and 3 of them could not be weaned from the mechanical ventilator and died. Three patients with intermediate syndrome who were not mechanically ventilated died due to delay for endotracheal intubation. The reasons for mortality for the other patients who died before intubation were as follows: one failure to intubate, and sudden respiratory and cardiac arrest (asystole) in four patients. Abnormal laboratory values were elevated liver enzymes, elevated lactate dehyrogenase, elevated blood glucose and leukocytosis (Table 3). Complications were observed in 35 (74.4%) patients: respiratory failure (14 patients), aspiration pneumonia (10 patients), urinary system infection (6 patients), convulsion (4 patients) and septic shock (1 patient). The duration of the intensive care stay was 5.2 ± 3.0 days.

Table 1

Organophosphate insecticide agents responsible for the poisonings

Agent	Number of patients
Dichlorvos	24 (51.1%)
Ethyl-Parathion	5 (10.6%)
Fenthion	4 (8.5%)
Chlorpyrifos	3 (6.3%)
Azinphos-methyl	3 (6.3%)
Diazinon	3 (6.3%)
Methamidophos	2 (4.2%)
Ethion	1 (2.1%)
Malathion	1 (2.1%)
Dictrophos	1 (2.1%)
Total	47 (100%)

Table 2

Clinical signs and symptoms of the patients

Sign or symptom	Number of patients
Meiosis	37 (78%)
Depressed mental status	36 (76%)
Hypersalivation	31 (66%)
Agitation	26 (55%)
Fasciculation	23 (49%)
Tachycardia	12 (25%)
Nausea	12 (25%)
Bradicardia	11 (23%)
Muscle weakness	9 (19%)
Vomiting	7 (15%)
Diarrhea	5 (10%)
Midriasis	3 (6%)

Discussion

OP compounds are used worldwide in agriculture as well as in household gardens [9]. This easy availability of the compounds has resulted in a gradual increase in accidental and suicidal poisoning, mainly in developing countries [10]. Ingestion of OP in an attempt at suicide is a major problem, especially for developing countries, probably because of the wide availability of pesticides as result of extensive use in agriculture and because of sale of these items over the counter in these countries [1]. OP poisoning due to suicidal attempt accounts for at least 40–60% of all cases in some African countries [10,11]. In this study, our rate of suicidal poisoning is 68%, probably because of the uncontrolled sale and use of these agents all over the country.

The inhibition of cholinesterase activity leads to the accumulation of acetylcholine at synapses, causing overstimulation of both central and peripheral nervous systems. Exposure to OP will interfere with synaptic transmission peripherally at muscarinic receptors and nicotinic receptors. Nicotinic manifestations include increased or decreased muscle power and skeletal muscle fasciculations. Muscarinic manifestations include excessive salivation, meiosis and diarrhea. The most frequent signs are reported to be meiosis, vomiting, hypersalivation, respiratory distress, abdominal pain, and depressed level of consciousness and muscle fasciculation [10]. In the present case series, the most frequent signs were meiosis, a depressed level of consciousness, hypersalivation, agitation and fasciculations.

Hyperglycemia has been reported many times in the literature [10,12,13], and we also observed mild hyperglycemia in 15 patients. The increase in serum glucose is believed to be due to secondary release of catecholamines from the adrenal medulla [14]. We observed 11 patients that had abnormal aspartate aminotransferase levels, which is reported very rarely [15]. OP compounds contain many solvents that may cause this effect. High lactate dehydrogenase levels may be associated with oxidative tissue damage induced by OP insecticides [16], and this level was high in 15 of our patients. Leukocytosis, which we observed in 34 patients, both with and without a left shift has been reported many times [10,14,17].

Table 3

Abnormal laboratory findings of the patients

	Normal values	Patient values
Aspartate aminotransferase (U/l)	0–50	53.7 ± 84.3
Lactate dehydrogenase (U/l)	225–450	548.8 ± 45.5
White blood cell count	4000–10,000	13,857 ± 7040
Blood glucose (mg/dl)	70–110	131 ± 61.9

Pralidoxime could not be given to 14 of the total patients since the Ministry of Health offices were out of pralidoxime. Pralidoxime was not given to two patients because they were admitted to the hospital 48 and 96 hours after OP poisoning, which was assessed as delayed time for pralidoxime administration. These two patients were treated successfully with atropine alone. OP compounds either have two ethyl ester or two methyl ester groups. Reactivation of dimethyl phosphorylated acetylcholinesterase proceeds quite rapidly and may improve without oxime therapy, although reactivation of diethyl phosphorylated acetylcolinesterase does not occur unless significant amounts of oximes are used. Two patients who died and did not receive pralidoxime were exposed to dichlorvos, which has two methyl ester groups. One patient who died and did not receive pralidoxime was exposed to parathion, which has one ethyl ester group. The major pharmacological action of oximes such as pralidoxime and obidoxime is to reactivate acetyl cholinesterase by removal of the phosphate group bound to the esteratic site [18]. Oximes should be given as soon as possible before aging takes place, but it is reported that there is beneficial response as long as 24 hours after exposure [9]. Oximes are believed to be effective, and to be especially useful in treating moderate or severe OP poisoning [2]. Oximes may also reverse the central nervous system effects of OP [2].

There has been only one placebo-controlled trial regarding oxime treatment for OP poisonings [19], which showed that pralidoxime + atropine does not have any benefit over atropine alone in OP poisonings. The need for mechanical ventilation, median days on mechanical ventilation, median days in the intensive care unit, frequency of the intermediate syndrome and the mortality rate are reported to be similar in each group [19]. In the present study, we observed that mortality is not significantly different whether or not the patients are treated with pralidoxime sulfate. This observation is also confirmed by the study of De Silva *et al* [19] but, since the data is still limited, we strongly suggest using pralidoxime. This issue needs further controlled studies. Our mortality rate (27.6%) is higher compared with series reported for OP insecticide poisoning and intensive care management [18,19]. In these two studies [18,19], the mortality rates were reported to be 12 and 16%, respectively. Our patients were admitted to the hospital 9.4 hours later than the exposure, and this relatively delayed admission might be a factor for the high mortality rate of our cases. We should implement a well-programmed emergency medical system that we currently do not have, and education of the general practitioners regarding intoxications needs to be improved.

Intermediate syndrome is a state of muscle paralysis that occurs after recovery from cholinergic crisis but before the expected onset of the delayed polyneuropath, and probably results from post-synaptic neuromuscular junction dysfunction [20]. Patients with intermediate syndrome require optimal respiratory management, atropine and pralidoxime. Three patients with intermediate syndrome did not receive pralidoxime and two of these patients eventually died. The rate of intermediate syndrome of our cases was 19.1%, with 4 of the patients intubated and mechanically ventilated, but 3 patients could not be weaned from the mechanical ventilator and died. Three of the cases with intermediate syndrome died due to delay for endotracheal intubation. After these events, we increased the nurse to patient ratio and the number of the residents in the unit because it was obvious that these cases had severe respiratory distress requiring endotracheal intubation before they died.

The mean respiratory rate increased from 22 ± 6 breaths/min to 38 ± 8 breaths/min, which is an obvious sign of respiratory failure, during the last 6 hours of hospitalisation. It has been reported previously that prolonged respiratory support and difficult weaning may be a consequence of intermediate syndrome [11]. Patients with intermediate syndrome may be followed with oxygen support without intubation and mechanical ventilation, but hypoxia and signs of respiratory failure such as tachypnea, paradoxical respiration and vigorous use of accessory respiratory muscles should be followed closely. Observation of any of these signs by an intensive care physician must lead to an assessment of the patient for endotracheal intubation and mechanical ventilation. The mortality rate was 50% for the patients who were mechanically ventilated, although it was 21.6% for the patients who are not mechanically ventilated and the difference is not statistically important ($P > 0.05$). The most troublesome complication was respiratory failure, which was observed in 29.7% (14) of our patients. Three of these patients died due to delay for endotracheal intubation. Four of our patients died due to sudden respiratory and cardiac arrest, which may be the first indication of unsuspected or incipient respiratory failure. Patients with OP poisoning may have respiratory failure for many reasons, including aspiration of gastric contents, excessive secretions, pneumonia and septicemia complicating adult

respiratory distress syndrome [21]. Aspiration pneumonia is another troublesome complication, and careful monitoring during transport and early recognition of an absent gag reflex may reduce the incidence of aspiration pneumonia. Early recognition of respiratory failure, prompt endotracheal intubation and mechanical ventilation are life-saving measures in severe OP poisoning.

In conclusion, OP insecticide poisoning is a serious condition that needs rapid diagnosis and treatment. Since respiratory failure is the major reason for mortality, careful monitoring, appropriate management and early recognition of this complication may decrease the mortality rate among these patients.

Competing interests

None declared.

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