Organophosphate Poisoning: A Multihospital Survey

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Abstract

Background: Organophosphates are frequently used as insecticides in the household and in agricultural areas, thus posing a risk for accidental exposure.

Objectives: To describe the characteristics, clinical course and outcome of 97 patients admitted to emergency rooms with a diagnosis of acute OP poisoning.

Methods: The clinical details of 97 patients were collected from 6 different hospitals in Israel. Diagnosis of intoxication was based on clinical findings, butyrylcholinesterase levels and, in several cases, the material brought to the hospital. Demographic, intoxication and clinical data were analyzed.

Results: The study group comprised 64 men and 33 women whose age range was 1–70 years (mean 19.8 $\pm$ 17.1); more than one-third of the patients were less than 10 years old. Accidental exposure was the cause of intoxication in 51.5% of the patients, and suicide in 20.6% of exposures. Intoxication occurred at home in most patients (67%), and the route of intoxication was oral in 65% of them. The patients arrived at the hospital 20 minutes to 72 hours after intoxication. Nine patients were asymptomatic; 53 presented with mild intoxication, 22 with moderate, and 13 had severe intoxication, 5 of whom died. There was a direct correlation between the degree of inhibition of butyrylcholinesterase levels and the severity of intoxication. Treatment included decontamination and antidotal medication. Duration of hospitalization ranged between 1 and 14 days (average 2.9 days).

Conclusions: Organophosphates may cause severe morbidity and mortality. Medical staff should therefore be aware of the clinical manifestations and the antidotal treatment for this poisoning.

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Organophosphate pesticides are widely used in modern agriculture. Their mode of action is irreversible inhibition of the enzyme cholinesterase. Acute OP intoxication causes accumulation of the neurotransmitter acetylcholine at the post-synaptic receptor sites, resulting in persistent cholinergic stimulation. Muscarinic activation causes miosis, nausea, vomiting, diarrhea, salivation, lacrimation, diaphoresis, secretions in the respiratory and gastrointestinal tracts, and incontinence. Nicotinic activation causes muscle fasciculation, weakness and paralysis. Activation of acetylcholine receptors in the central nervous system results in confusion, decreased consciousness, seizures and respiratory depression. Therefore, exposure to high doses of OP may cause severe morbidity and mortality. Treatment consists of termination of the exposure by decontamination and gastric lavage, antidotal therapy with atropine and oximes, and supportive therapy with benzodiazepines and mechanical ventilation [1,2].

Worldwide, intoxication attributed to pesticides has been estimated to be as high as 3 million cases of acute, severe poisoning a year. The exposure can be accidental or suicidal, occupational, bystander exposure, or exposure of the general public who consume food items containing pesticide residues [1,2].

We present a multihospital study of Israeli patients with OP intoxication, their characteristics, severity of poisoning, course of disease and treatment.

Patients and Methods

Ninety-seven patients from 6 different hospitals in Israel who were admitted due to OP poisoning during the years 1979 to 1997 were studied.

Data collection

All hospitals in Israel were requested to participate in a screening study of all pesticide intoxications that led to hospitalization in the last 10 years. Six hospitals from the center and south of Israel (Meir, Hadassah Mount Scopus, Shaarei Zedek, Wolfson, and Soroka) agreed to cooperate in the study. Data were collected from medical files, searched using each hospital's specific codes for pesticide poisoning. Only hospitalized patients were included in the study. Information regarding gender, age, religion, cause of intoxication, signs and severity of intoxication, butyrylcholinesterase levels, treatment and outcome of the patients was analyzed.

Severity of intoxication

Mild intoxications were defined by symptoms of miosis, rhinorrhea, lacrimation, and mild abdominal pain, without difficulties in respiration and without disturbances of consciousness. Moderate cases were defined as having aggravation of the latter symptoms with additional complaints of the respiratory and gastrointestinal systems. Severe cases were defined as having, in addition to the previous symptoms, loss of consciousness, convulsions or respiratory depression.

Butyrylcholinesterase

Butyryl (pseudo) choline esterase, rather than acetylcholinesterase, inhibition was analyzed. Most hospitals measure only butyrylcholinesterase activity in the serum, after centrifugation and removal of the red blood cells. Only in special cases do hospitals send blood samples for the assessment of acetylcholinesterase activity to the Toxicology Unit at the Sheba Medical Center, which has the ability to measure acetylcholinesterase activity in the red blood cells.

The degree of inhibition of butyrylcholinesterase was calculated based on the following formulae:

$$\% \text{ inhibition} = \frac{\text{lower normal level of the laboratory} - \text{blood level of patient}}{\text{lower normal level of laboratory}} \times 100$$

OP= organophosphate

Table 1. Gender, severity of injury and cause of intoxication in different age groups

		Gender		Severity of injury					Cause of intoxication			
Age category	Total	Male	Female	Asymptomatic	Mild	Moderate	Severe	Dead	Suicide	Occupational	Accidental	Unknown
0–10	35	19	16	6	17	10	2	0	0	0	30	5
10–20	22	14	8	0	11	4	3	4	6	1	10	5
20–50	36	29	7	2	24	7	2	1	14	10	7	5
50–80	4	2	2	0	2	1	1	0	0	1	3	0
total	97	64 (66%)	33 (34%)	8 (8%)	54 (55.7%)	22 (22.7%)	8 (8%)	5 (5.6%)	20 (20.6%)	12 (12.4%)	50 (51.5%)	15 (15.5%)

Table 2. Clinical manifestations and BchE levels

Severity of injury	No. of patients	% BchE inhibition (mean)	Miosis No. (%)	Lacrimation No. (%)	Sweat No. (%)	Rhinorrhea No. (%)	Salivation No. (%)	Gastro-intestinal No. (%)	Respiratory No. (%)	Fasciculations No. (%)	Loss of consciousness No. (%)	Convulsions No. (%)
Asymptomatic	9	0	0 (0)	0 (0)	0 (0)	1 (11)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Mild	53	55.92	27 (51)	3 (6)	23 (43)	4 (8)	18 (34)	27 (51)	17 (32)	12 (23)	0 (0)	0 (0)
Moderate	22	76.51	18 (82)	3 (14)	8 (36)	3 (14)	17 (77)	11 (51)	18 (82)	11 (45)	0 (0)	0 (0)
Severe	8	86.11	5 (63)	0 (0)	3 (38)	0 (0)	4 (51)	5 (63)	8(100)	6 (75)	8 (100)	7 (88)
Dead	5	87.44	3 (61)	0 (0)	1 (20)	0 (0)	2 (40)	2 (40)	5(100)	3 (61)	5 (100)	4 (80)
Total (%)	97 (100)	59.52	53 (54.64)	6 (6.18)	35 (36)	8 (8.24)	41 (42.2)	45 (46.4)	48 (49.48)	31 (32)	13 (13.4)	11 (11.34)

The degree of butyrylcholinesterase levels presented here are those at admission to the hospital.

Results

General data

Sixty-four men and 33 women were admitted to six different hospitals during the period of the study (1979–1997). Sixty-six were Muslims and 31 were Jews. Age range was 1–70 years old (mean 19.8 $\pm$ 17.1), and 38 patients (39%) were less than 10 years old. The distribution of age categories, gender, cause and severity of intoxication are described in Table 1.

Intoxicating agent

The insecticide causing intoxication was a phosphothion agent in 38 patients, and a phosphoxon agent in 10. The poison was unknown in 48 cases (49.5%). Household insecticides were the cause of intoxication in 64% of the known cases, and agricultural pesticides were the cause of intoxication in 36% of these cases.

The cause of exposure was accidental in 50 patients, a suicide attempt in 20, occupational in 12 and unknown in 15 patients [Table 1]. Accident was the cause of intoxication in all the patients under the age of 10. Most occupational exposures occurred between the ages 20 and 40, all of them in men. More men used the agent to commit suicide than women (22% compared to 18% respectively), but more women were accidentally intoxicated (67% compared to 44% respectively).

The route of intoxication was oral in 63 patients, inhalational in 8, dermal in 6, combined inhalational and dermal in 6, and combined inhalational and oral in 2 patients.

Sixty-four patients were exposed to the pesticide at home, 19 in the field, and 2 in other workplaces. Most patients arrived at the hospital within 3 hours of intoxication. Time to arrival ranged from 20 minutes to 72 hours after the exposure (average 6.9 hours post-exposure).

Clinical manifestations

Nine patients were asymptomatic when admitted to the hospital, 53 presented with mild OP intoxication, 22 with moderate intoxication, and 13 with severe intoxication; 5 of the 13 died during hospitalization [Table 1]. The clinical manifestations of the patients as well as the degree of butyrylcholinesterase inhibition are summarized in Table 2. Sweating, blurred vision due to miosis, nausea, vomiting, diarrhea, shortness of breath and wheezing were the most common complaints. Inhibition of butyrylcholinesterase was increased as the severity of the intoxication worsened [Table 3].

Treatment and outcome

In general, the treatment protocol in all hospitals was based on the current guidelines of organophosphate poisoning [1,2]. Table 4 summarizes the average dose of medications for the different stages of intoxication. Termination of exposure to the OP was achieved by decontamination using water and soap (in 13 patients), and by removal of the material from the gastrointestinal system using ipecacacuanha syrup for the conscious patients, or by gastric lavage with instillation of charcoal for the unconscious patients. Therapy consisted of repeated doses of atropine in all treated patients, oximes (mainly toxogonin) and diazepam as an anxiolytic and anticonvulsant, as is generally accepted. Fourteen patients were mechanically ventilated. The duration of ventilation ranged from 2 to 22 hours (average 7.6 hours). The duration of hospitalization ranged between 1 and 14 days (average 2.9 days) [Table 4].

Table 3. Butyrylcholinesterase levels and clinical manifestations

	Degree of BchE inhibition		
	0–50%	51–85%	86–100%
Asymtomatic	100%	0%	0%
Mild	38%	31%	31%
Moderate	5%	58%	37%
Severe	0%	50%	50%
Dead	0%	33%	67%

Table 4. Severity of intoxication, accumulated doses of medications and duration of hospitalization average dose (range)

Severity of injury	No. of patients (total)	Atropine (mg)	Toxogonin* (mg)	Diazepam (mg)	Scopolamine (mg)	Duration of hospitalization (days)
Asymptomatic	9	0.5 (0.5–0.5)	125 (125–125)	0.00		1.00
Mild	53	5 (0.5–26)	624 (20–2,350)	9 (5–17)		1.9 (0–6)
Moderate	22	26 (0.2–74)	1029 (68–3,375)	21 (1–50)		3.36 (1–7)
Severe	8	32 (1–150)	1283 (50–3,130)	53 (4–110)		7.13 (2–10)
Dead	5	149 (2–689)	3476 (1,000–8,500)	515 (74–1,087)	0.75	7.6 (0–14)

* Only one patient, moderately injured, received pralidoxime in a total amount of 1,250 mg

Clinical manifestations of the deceased patients

Two women and three men had severe intoxication that led to their death. Four of them were less than 20 years old. The route of intoxication was oral in all of them, and accidental in four (one patient committed suicide). All were unconscious when admitted, with respiratory depression. They were treated with large amounts of antidotes, but death was determined 36 minutes to 14 hours after admission.

Discussion

Organophosphates are widely used in the household and in agriculture. Intoxication with organophosphates is a worldwide problem and may cause severe morbidity and mortality [3]. We describe 97 patients from 6 different hospitals in Israel who were exposed to and intoxicated by OP. The relatively small number of poisoned patients derives from the fact that only six hospitals from the south and the center of Israel participated in the study, and only hospitalized patients were analyzed. Nevertheless, these hospitals are representative as they serve urban as well as agricultural populations in Israel.

Most of the patients were men, although the main causes of intoxication were accidental and suicidal and not agricultural. The ratio between men and women varies between the different studies, ranging from 6.14 [4] to 0.14 [5]. The average age in our series was in accordance with the literature, the majority being less than 30 years old [4–6]. The majority of the intoxications was accidental, most of them occurring in children and in women in the household. As described before [7], all children in whom the route of intoxication was known were accidentally poisoned. All occupational exposures were in men, most of whom were 20–40 years old. Suicide attempts occurred in 20.6% of the patients, with a similar frequency between men and women. Similar to our findings, Adlakha et al. [6] found that most of the exposures (62%) were accidental, but the majority occurred in men during occupational exposure. Delilkan et al. [5], however, found that 98% of the intoxication cases in the intensive care unit were the result of suicide attempts, the majority (88%) being women. These differences may be explained by the assumption that in the case of intentional exposure to poison, as in suicide attempts, the amount of the poison ingested is usually larger than in accidental exposure when the taste or smell of the material may halt the patient from further exposure. Thus, most of the organophosphate suicide attempts were admitted to the intensive care unit. In the study of Karalliedde and Senanayake [4], most of the intoxication events were also suicidal but the majority (86%) occurred in men.

The insecticide agent was unknown in nearly half the patients in our study, and diagnosis was based on clinical findings and low butyrylcholinesterase levels. This may be due to the fact that most of the cases occurred at home and in children, and the patients did not know the exact pesticide with which they were poisoned. Similarly, Adlakha et al. [6] and Tabershow and Cooper [8] reported 46% and 57% respectively of poisoned patients in which the exact material was unknown. When the cause of the poisoning was known, most of the cases were due to phosphothion intoxications (as malathion, parathion or dimethoate) in accordance with the literature [4]. The route of intoxication was oral in the vast majority of our cases, possibly due to the high frequency of accidental exposure, especially in children [9,10].

Butyrylcholinesterase levels as well as clinical findings were used as a means of diagnosis of the intoxication. As expected, the degree of inhibition increased as the clinical manifestations worsened. It is worth noting that the butyrylcholinesterase inhibition was higher than 86% in 37% of the moderately affected patients, and between 51 and 86% in 50% of the severe cases. Even in the patients who died, only 67% had a high degree of butyrylcholinesterase inhibition (above 86%). Red blood cell acetylcholinesterase is an enzyme similar to the acetylcholinesterase in the synapse, therefore it may be a more reliable indicator for the severity of the intoxication. However, since the degree of its inhibition becomes maximal a few hours after the intoxication, it cannot serve as an indicator for the severity of the intoxication immediately after it occurs. Plasma butyrylcholinesterase is inhibited immediately after the intoxication, but there is no relation between its activity or inhibition and the acetylcholinesterase activity or inhibition. The reactivation of butyrylcholinesterase in the plasma lasts a few hours, while in the synapse it lasts a few days, and in the red blood cells a few weeks. Therefore, although butyrylcholinesterase may be used in the early diagnosis of OP intoxication, its inhibition should not be used to predict or serve as a measure of the severity of the intoxication, as mentioned in previous studies [11]. It is important to mention that butyrylcholinesterase levels are low in children, and in burns, malignancies, sepsis, and diseases of the liver or kidney [12].

As reported previously [4–6,10–16], our patients presented with cholinergic signs and symptoms, especially miosis, sweating, hypersalivation and complaints of the gastrointestinal or respiratory systems. The number and intensity of the clinical manifestations increased as the severity of the intoxication worsened. This correlation is in accordance with previous works [5,7,17,18].

Treatment consisted of decontamination, administration of anticholinergic drugs, oximes, and supportive care as accepted [12,15,19]. As expected, the average dose of medications increased as the intoxication worsened. Mild cases of OP intoxications may resolve without any antidotal treatment [20]. On the other hand, severe cases may necessitate a large amount of medications – up to 1,300 mg atropine in the report of Bardin et al. [18], 1,740 mg in the report of Adlakha et al. [6], and even 19,590 mg in a case report of parathion poisoning [21]. In our study, the largest amount of atropine used was 689 mg. Repeated doses of the oxime toxogonin were given to the moderate and severe cases, because of the drug's ability to reactivate acetylcholinesterase.

In intoxication by an OP used in the household or in agriculture, the inhibited acetylcholinesterase does not undergo aging. Aging is a chemical reaction of the inhibited acetylcholinesterase that includes the creation of a negative electric pole on the complex enzyme poison, which prevents the reactivation of the inhibited enzyme by oximes (due to electric rejection and higher thermodynamic stability of the complex). Since there is no aging in agricultural OP intoxication, treatment with oximes in repeated doses even for days may be beneficial in reactivating the inhibited enzyme.

Organophosphates are lipophilic and may be accumulated in different tissues in the body. Due to their release from these tissues to the bloodstream, the clinical manifestations, especially in severe cases, may be prolonged and include relapses. One of the possible sequelae of OP poisoning may be paralysis of the diaphragm [22] or larynx [23], which may cause difficulties in extubation. In the 14 patients in our study who were mechanically ventilated (5 of whom died), the duration of the mechanical ventilation ranged from 2 to 22 hours (average 7.6 hours), with no report of paralysis of the respiratory muscles. The low incidence of mortality in our group (5%) has been reported before [5], and may be attributed to the well-organized medical facilities and the increasing experience of the medical staff in the diagnosis and treatment of poisonings. The duration of hospitalization ranged as expected from only 1 day for the mild cases to 14 days for the severe cases. Longer periods of hospitalization have been documented [17,24] and may even reach 37 days [25] or even 3 months [21] due to prolonged duration of mechanical ventilation.

Organophosphates may cause long-term morbidity after the acute phase of the poisoning, mainly in the cardiovascular system and in the central nervous system [15,22,23]. No late sequelae were reported in our patients during hospitalization, but no long-term follow-up was conducted.

In summary, we have described an intoxication that may be life-threatening, caused mostly by accident especially in small children, but may be avoided by careful supervision of the child and careful handling of pesticides at home or at work.

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