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Review of clinical and toxicological features of acute pesticide poisonings in Crete (Greece) during the period 1991–2001

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background: In Crete, the largest island of Greece, many pesticide formulations are increasingly used in agriculture in order to raise crop production. This study reviews a number of pesticide poisoning cases registered at the Center of Toxicology and Forensic Sciences Research at the University of Crete between 1991 and 2001.

Material/Methods: The medical records and toxicological data of the pesticide poisonings are presented. The analyzed samples were mainly blood and/or urine, but also gastric fluids and other tissues. Analysis involved a variety of techniques.

Results: Eleven poisonings caused by paraquat (7 men, 4 women, aged 15–58 years) are reported, five of which had fatal outcome. Initial paraquat plasma levels ranged between 0.4–165 μg/ml. Thirteen intoxications due to various organophosphorous agents are presented (11 men, 2 women, aged 13–69 years). Pesticide blood levels upon admission ranged from 1.0–108 μg/ml and there were six fatalities. Carbamate poisonings (4 men, 2 women, aged 32–60 years) were caused by methomyl (initial blood levels 1.6–57 mg/l) and resulted in death. A case of methyl bromide intoxication is also presented.

Conclusions: The results of the study highlight the toxic and potentially lethal effects of pesticide formulations used in agriculture. Special seminars should be run to educate farmers on the proper use of these agents and the supply of pesticides should be restricted to those who follow all safety measures. Physicians should be trained to promptly identify and treat pesticide intoxications.

key words: **pesticide poisoning • paraquat • organophosphates • carbamates • Greece**

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BACKGROUND

In current years, many different active ingredients and thousands of formulations are used in agriculture to control pests and disease-carrying vectors [1]. It is estimated that 1½ million tones of pesticides are manufactured every year, producing a business worth US $30 billion [2]. Due to the extensive use of these agents, pesticide poisoning remains one of the major health issues in both developing and developed communities [3–5].

Data coming from the National Center of Poisonings in Greece show that although the prevalence of pesticide poisonings as a proportion to the total number of poisonings decreased from 5.9% in 1988 to 3.6% in 1999, the actual number of pesticide poisonings increased during the same time period from 1193 to 1700 cases per year (Figure 1) [6]. Fatalities from pesticide poisonings also increased. Of the total number of poisonings registered, only 12% were suicide attempts, and the remaining cases were due to occupational (40%) or accidental (45%) exposure.

The island of Crete, located in the southern part of Greece, has a population of approximately 650,000 people, involved mostly in agriculture. As a result, pesticides are widely used to increase production and raise crop quality, and there are many cases of intoxication caused either by accident or on purpose.

This study is a review of previously published acute pesticide poisonings registered at the Center of Toxicology, University of Crete School of Medicine, over a 10-year period (1991–2001). These are cases that were fully investigated and were selected on the basis of their clinical and toxicological interest. They include intoxications caused by intentional or unintentional (accidental or occupational) exposure to organophosphorous and carbamate agents, paraquat, and methyl bromide [7–15]. The aim of the study is to present an overview of the clinical and laboratory data of the poisoning cases, discuss their treatment options, and highlight the potential life-threatening effect of exposure to pesticides.

MATERIALS AND METHODS

All toxicological investigations were performed at the Center of Toxicology and Forensic Sciences Research of the University of Crete, which serves the whole island of Crete. The choice of specimens was the responsibility of the physicians or pathologists working in collaboration with toxicologists. The samples were mainly blood and/or urine, but also gastric fluids, hairs and post-mortem tissue. Analysis involved a variety of techniques. General toxicological screening included headspace gas chromatography (GC) for volatiles, immunoassays techniques (Abbott TDx and ADx) and automated liquid chromatography REMEDI HS Drug Profiling System (BIO-RAD Labs, USA) for basic, amphoteric and acidic drugs, and color tests for chemicals. Confirmation and quantitative analysis employed GC, high-pressure liquid chromatography (HPLC), and mass spectrometry (MS); details on the analytical procedures are given elsewhere [8–12,14]. Quantitative estimation of blood and serum cholinesterase activity and of paraquat in fluids was done spectrophotometrically with reference values 3,500–8,500 U/l [8,10]. Determination of low serum and urine paraquat concentrations (<0.1 μg/ml) were conducted on a Spectra Physics Liquid Chromatographer (SP8810) connected with UV-Vis detector (SP8450) and SP4270 integrating recorder [10].

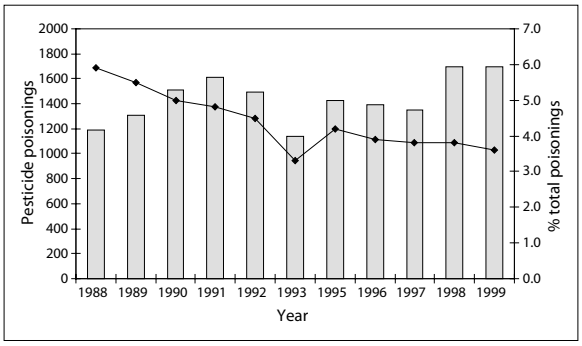

Figure 1. Pesticide poisonings cases (actual number and% proportion of the total poisonings) encountered in Greece during 1988–1999.

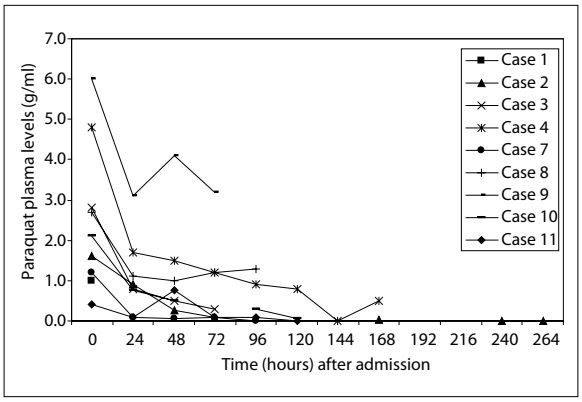

Figure 2. Time course of paraquat blood levels during hospitalization of 9 poisoning cases registered in Crete during 1991–2001.

RESULTS

Paraquat poisoning cases

The clinical and toxicological data of eleven paraquat poisonings during 1991–2001 are presented in Table 1. There were 7 men and 4 women aged 15–58 years old. Six cases were suicide attempts with ingestion of the compound. Of the remaining cases, four were caused by accidental ingestion and one by transdermal absorption of the sprayed pesticide. The latter case involved a 31-year-old male farmer who presented with painful skin irritations in the lumbar and intergluteal regions after having sprayed with paraquat for three consecutive days. After treatment of the dermatitis and cleaning of the infected area, the patient took a urine color test that was positive for paraquat and he was immediately referred to the nephrology department. In all other cases, presenting symptoms were gastrointenstinal distress (nausea, abdominal pain, vomiting, diarrhea) and oro-pharyngeal irritation. Two of those who attempted suicide were found dead with paraquat plasma levels of 73 and 154 μg/ml. Treatment included gastric lavage with water and activated charcoal, bentonite, intravenous fluids with manni-

Table 1. Clinical and toxicological data of eleven paraquat poisoning cases encountered in Crete during 1991–2001.

Case	Sex	Age (years)	Quantity of paraquat solution (ml)	Delay in presentation (hours)	Initial paraquat plasma levels (µg/ml)	Treatment*	Length of therapy (days)	Outcome
1	F	15	150**	2	1.0	HP	40	Survival
2	F	52	5–10	6	1.6	HP-PL	10	Survival
3	M	58	5–10	41	2.8	HP	4	Death
4***	F	16	80–100	2½	4.8	HP	28	Survival
5	M	43	>150	–#	165	–	–	Death
6	F	38	>150	–#	73	–	–	Death
7	M	36	5–10	8	1.2	HP	7	Survival
8	M	49	20–30	6	2.7	HP	4	Death
9	M	33	150	7	6.0	HP-HD	3	Death
10	M	22	30–40	2	2.1	HP-HD	16	Survival
11	M	31	–##	4	0.4	HP-HD	14	Survival

* standard treatment included gastric lavage and bentonite if recent pesticide ingestion, administration of intravenous fluids and mannitol (HP – hemoperfusion; PL – plasmapheresis; HD – hemodialysis);
** multiple vomiting episodes following the ingestion of paraquat solution;
*** cases 4-9 were suicide attempts;
# was found dead;
transdermal absorption of paraquat

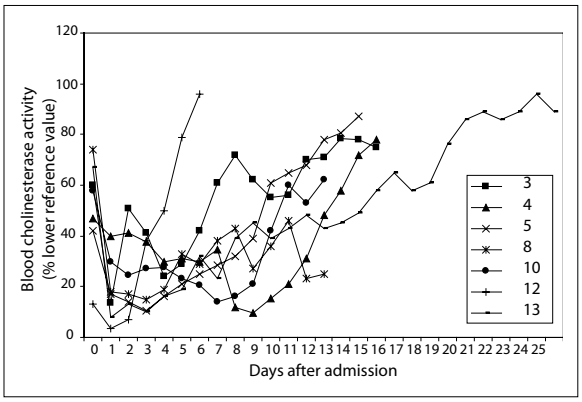

Figure 3. Time course of blood cholinesterase activity (% lower reference value) during hospitalization of 7 organophosphorous poisoning cases registered in Crete during 1991–2001.

tol, and hemoperfusion and/or plasmapheresis or hemodialysis sessions. Those who survived from the intoxication (n=6) remained hospitalized for 7–40 days. The time course of paraquat plasma levels during therapy and before each hemoperfusion session is shown in Figure 2.

Organophosphorous poisoning cases

Thirteen poisoning cases caused by various organophosphorous agents (fenthion, n=4; methidathion, n=3; dimethoate, n=2; omethoate, n=1; malathion, n=1; phosphamidon, n=1; mecarbam, n=1) are presented. The main demographic and toxicological data are summarized in Table 2. There were 11 men and 2 women aged 13–74 years old. All cases were suicide attempts except for that of a 30-year-old man who mistakenly used fenthion to prepare coffee and that of a 13-year-old boy who was poisoned due to transdermal absorption and inhalation of fenthion. The ingested amount of the pesticide solution in five of the suicide cases ranged between 150–250ml. Five of those who attempted suicide had a history of excessive alcohol consumption or psychiatric disorder. The clinical presentation typically included weakness, decreased muscle tone and/or deep tendon reflexes, hypotension, bradycardia, respiratory distress, and altered level of consciousness. The 13-year-old child (case 12) was engaged with adults spraying their fields with fenthion for seven consecutive days and presented with fatigue, abdominal pain, and a fainting episode. He then experienced a seizure episode, developed respiratory distress, and was admitted to the intensive care unit. Patients were treated with gastric lavage (water and activated charcoal), enemas with lactulose, intravenous fluids, atropine and pralidoxime (2-PAM). The 13-year-old child also received a gastric lavage on a routine basis since the route of intoxication was not certain, and a whole-body skin washing. Most patients required mechanical ventilation, and the length of hospitalization ranged from 3–45 days for those who survived the poisoning (n=7). The time courses of blood cholinesterase activity (7 cases) during treatment are presented in Figure 3.

Carbamate poisoning cases

We present six acute poisoning cases caused by the carbamate methomyl. These include 2 women and 4 men aged 32–60 years old (Table 2). In five cases the cause of intoxication

Table 2. Clinical and toxicological data of selected organophosphorous (n=13) and carbamate (n=6) poisoning cases encountered in Crete during 1991–2001.

Case	Sex	Age	Pesticide	Initial pesticide blood level (μg/ml)	Initial ChE activity (U/l)	Management*		Outcome
						Mechanical ventilation	PAM	
Organophosphorous poisonings								
1	F	63	Fenthion	2.9	350	+	+	Survival
2	M	30	Omethoate	1.6	900	–	+	Survival
3	M	60	Dimethoate	9.3	480	+	+	Survival
4	M	47	Methidathion	2.8	1400	+	+	Survival
5	M	42	Dimethoate	52.3	595	+	+	Survival
6	M	69	Fenthion	4.8	–**			Death***
7	F	36	Malathion	108.0	–			Death#
8	M	74	Methidathion	6.2	630	+	+	Death
9	M	70	Methidathion	3.3	–	–	–	Death
10	M	58	Mecarbam	16.3	1050	+	+	Death
11	M	40	Phosphamidon	40.0	–			Death#
12	M	13	Fenthion	1.0	124	+	+	Survival
13	M	67	Fenthion	2.7	250	+	+	Survival
Carbamate poisonings								
1	M	35	Methomyl	35.0	262			Death#
2	M	58	Methomyl	57.0	300			Death***
3	M	52	Methomyl	8.0	199			Death#
4	F	32	Methomyl	5.6	180			Death#
5	F	36	Methomyl	28.0	245	+	–	Death
6	M	60	Methomyl	1.6	380	+	–	Death

* the standard treatment included gastric lavage and/or enemas, atropine and intravenous fluids administration;
** not available;
*** died shortly (~2 hours) after admission or on the way to the hospital;
# was found dead

was ingestion of the pesticide in a suicide attempt. There was also a 60-year-old man (case 6), a farmer, who was poisoned due to inhalation and transdermal absorption of sprayed methomyl, which was not detected in gastric fluids. Methomyl blood concentrations ranged between 1.6–57.0 mg/l. Blood cholinesterase activity ranged between 2–70% of the normal blood cholinesterase activity values. Three of the victims were found dead and the remaining three in coma, one of whom died on the way to the hospital. Of the two patients admitted to the hospital, one (case 5) never regained consciousness and was diagnosed with brain death after 10 days, and the other (case 6) was treated with atropine but developed multiple-organ dysfunction syndrome and died within 3 days.

Other pesticide poisoning cases

A 43-year-old man was admitted to the hospital 1½ hours after he had tried to ingest and finally inhaled an unknown amount of methyl bromide (MeBr) solution. He complained of headache and giddiness. His blood pressure was 110/60 mmHg, heart rate 140 bpm, and body temperature 38°C. Soon his condition deteriorated and he was intubated. A gastric lavage was performed that yielded bloody fluid and the patient was transfused with whole blood. He developed convulsions, which were treated with imidazole. However, he became hemodynamically unstable, developed pulmonary edema, and died four hours after admission. The toxicological analysis showed that MeBr and inorganic-bromide concentrations in peripheral blood were 3.3 μg/g and 480 μg/ml, respectively.

Discussion

The present study summarizes the main clinical and toxicological findings of pesticide poisonings registered at the Center of Toxicology, University of Crete School of Medicine,

during the period 1991–2001. Paraquat, organophosphate, and carbamate agents were the most common pesticides encountered in these intoxication cases.

Paraquat, the 1,1′-dimethyl-4,4′-dipyridylium dichloride salt, is a herbicide used primarily for weed control [15]. In Greece it is marketed as a 20% aqueous solution under various trade names (Gramoxone, Zintox AS, Sinasil AS, Proxon, etc.). Although spraying paraquat under proper conditions is considered safe, fatal cases have been reported due to accidental or intentional exposure. Its toxicity is attributed to generation of oxygen free radicals causing lipid peroxidation and cell death [15,16]. Immediately after ingestion, signs and symptoms of gastrointenstinal distress (such as nausea, vomiting, diarrhea) occur as well as painful oro-pharyngeal erosions [17]. The results of our poisoning cases suggest that consumption of large amounts of paraquat solution (150–250 ml) results in death within a few hours, depending on various factors such as early or late vomiting, immediate management, and the presenting status of the patient. Moreover, ingestion of small but potent amounts of paraquat might also result in severe intoxication, even 2 days later, with fatal outcome (case 3). Due to the high mortality of paraquat poisoning, many prognostic indicators of the outcome have been attempted [18]. Using the survival curves described by Hart et al. [19], we found that all of our intoxications with fatal outcome belonged to survival probability levels <30%.

Early intervention is probably the most important determinant of survival in paraquat poisoning. To date there are no known pharmacological antagonists for paraquat and there are also no chelating agents capable of binding the poison in the blood or other tissues. As a result, strategies in the management of paraquat poisoning have been directed toward the modification of the toxicokinetics of the poison by either decreasing its absorption or enhancing its elimination. Such approaches are intended to prevent the accumulation of paraquat in tissues and include procedures such as induced emesis or diarrhea, gastric lavage, administration of oral absorbents, hemodialysis, and hemoperfusion [12,15,20]. Corticosteroids and other immunosuppressive agents have also been used. Recognizing that paraquat induces its toxic effects via oxidative stress-mediated mechanisms, innovations in the management of paraquat poisoning are directed towards the use of antioxidants such as superoxide dismutase and antioxidant vitamins [20]. One patient (case 1) was treated with prednisolone, vitamin E, and allopurinol because of respiratory complications and finally survived with findings of lung fibrosis, a well-described sequel of paraquat intoxication [21].

Organophosphate and carbamate insecticides are potent cholinesterase inhibitors causing muscarinic, nicotinic, and central nervous system (CNS) symptoms (cholinergic crisis). These include bronchospam and bronchorrhea, muscular fasciculations and weakness, bradycardia, dizziness, gastrointestinal distress, salivation and lacrimation. Interestingly, the 13-year-old boy (case 12), who was engaged with adults in spraying the organophosphate fenthion, presented only with gastrointestinal distress and a history of a fainting episode. This agrees with the reported differences in clinical presentation of cholinesterase inhibitor intoxication between adults and young children [22]. In children, the most common signs are hypotonia and CNS depression, and the absence of typical muscarinic effects cannot exclude the possibility of cholinesterase inhibitor poisoning.

With regard to organophosphates, two other types of neurotoxicity besides the acute cholinergic crisis have been described: 1) delayed neurotoxicity, a predominantly motor mono/poly-neuropathy arising approximately 2–3 weeks after exposure, attributed to inhibition of neuropathy target esterase (NTE), and 2) the intermediate syndrome, appearing 2–5 days after the acute crisis and characterized by acute respiratory muscles paresis, weakness of multiple motor cranial nerves, weakness of neck flexor and proximal limb muscles, and depressed tendon reflexes. It is caused by prolonged cholinesterase inhibition, resistant to atropine and oxime treatment. Delayed polyneuropathy was developed by our case patient 3 (a 60-year-old male), who ingested dimethoate and survived after staying hospitalized for 45 days. The intermediate syndrome was encountered in two of our organophosphate poisonings: case patient 4 (a 47-year-old male) who ingested methidathion, and case patient 5 (a 42-year-old male), who ingested dimethoate. They both survived after staying in the ICU for 15–24 days.

Methomyl toxicity studies have indicated that it is an extremely toxic pesticide with low chronic but high acute oral toxicity and a lethal dose of 12–15 mg/kg body weight [8,23]. The high toxicity of methomyl was confirmed by the results of our study, where all six victims had fatal outcome. Apart from the poisoning caused by gastrointenstinal absorption, the high potential of methomyl poisoning through inhalation or transdermal absorption has also been reported and this was demonstrated in our case patient 6 [13].

Besides skin and gastrointenstinal decontamination, treatment of cholinesterase inhibitor poisonings includes maintenance of open airway, oxygen supply, and administration of atropine in a relatively high dose, until pulmonary secretions are controlled [5,24]. Patients poisoned by organophosphate agents should also receive pralidoxime (2-PAM), which is a cholinesterase reactivator and thus a specific therapeutic agent. Although some reports have questioned the effects of oximes and their necessity in organophosphate poisoning [25,26], oximes may be beneficial even in cases of little effect on blood cholinesterase activity, as they have been shown to reduce diaphragmatic muscle necrosis in experimental intoxications [27]. In contrast, oxime therapy is not recommended for carbamate poisonings, since *in vitro* studies with carbaryl, another carbamate pesticide, have shown amplification of carbamate toxic effects by oximes [5,28].

With regard to MeBr, there is only limited literature and MeBr poisonings are mostly encountered in manufacturing facilities that produce or utilize it as a disinfectant agent [29]. In agriculture, poisonings are due to inhalation of MeBr gas or aerosol particles from fumigators [10,24]. MeBr is colorless and nearly odorless, but is severely irritating to the lower respiratory tract, sometimes inducing pulmonary edema, hemorrhage, or chemical pneumonia. Little is known of the mechanism of MeBr toxicity. It is suggested that it inhibits the glutathione-S-transferase activity in the brain and reduces catecholaminergic neuronal activity [10]. Early symptoms include headache, dizziness, nausea, vomi-

ting, tremor, slurred speech, and ataxia. More severe poisonings exhibit myoclonic and generalized tonic clonic seizures that are often refractory to treatment. Treatment is largely supportive and prognosis varies depending on the severity of the intoxication.

CONCLUSIONS

Despite their decreasing prevalence, the number of new pesticide poisonings per year has increased during the last decade, accounting for 3–4% of the annual intoxication cases in Greece [6]. The compounds of concern belong to the family of cholinesterase inhibitors (organophosphorous, carbamates) and the herbicide paraquat. Our results indicate that most intoxications are severe with high mortality rates. This is emphasized by the fact that many of the poisonings were caused by unintentional (occupational or accidental) exposure to the chemicals.

Initial management of intoxication should include decontamination procedures (skin washing, gastric lavage), administration of antidotes such as atropine and pralidoxime in the case of intoxication due to cholinesterase inhibitors, or hemodialysis-hemoperfusion in the case of paraquat poisoning.

Suggested measures include intensive training and education programs instituted by local agricultural unions to inform farmers of the proper use of pesticides and the precautions to be taken during their use [30,31]. Considering the common use of pesticide formulations in suicide attempts, it might be reasonable to make highly toxic pesticides available only in limited amounts and only to those who follow all safety guidelines. Finally, emergency and primary care physicians should have sufficient training to promptly identify and treat pesticide poisonings.

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