

## Research Article

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# Profile of adult acute cholinesterase inhibitors substances poisoning – a 30 years analysis

**Abstract:** Objectives: The objective of this study was to assess the pattern and outcome of acute cholinesterase inhibitors substances (CIS) poisoning cases, in a cohort from a regional tertiary care hospital. Methods: cases admitted in the Toxicology Clinic of “Sf. Spiridon” Emergency Clinic Hospital Iasi, Romania between 1983 and 2013 were studied. Results: a total number of 606 patients were included. The reason for exposures was intentional in 70% of cases and the commonest route of poisoning was oral in 92.2%. The highest percent of cases was females (56.4), the age group 20-29 (25.4%) and the majority (66.7%) coming from rural areas, 28.2% being agricultural workers. 36.6% of cases were severe clinical forms. Overall mortality rates were 3.8%, more than half of the death patients (65.2%) had concomitant alcohol intake. It was a significant statistical association between decrease level of serum cholinesterase on admittance and severe forms ( $p < 0.000$ ) and between survival and deaths groups ( $p < 0.000$ ). The pattern of poisoning described by our retrospective study suggests that CIS poisoning are mainly preventable. The main effective goals for prevention are restriction in free accessibility to toxic pesticides, together with sustained efforts in education concerning the life-threatening danger of pesticide poisoning.

**Keywords:** Epidemiology, pesticide, toxicity

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## 1 Introduction

Cholinesterase inhibitors substances (CIS) are chemicals whose primary toxic effect is to block the normal breakdown of the acetylcholine, thereby increasing both the level and duration of action of the neurotransmitter. The two main classes of cholinesterase inhibiting pesticides are the organophosphates and the carbamates. Some newer chemicals, such as the chlorinated derivatives of nicotine can also affect the cholinesterase enzyme.

Acute cholinesterase inhibitors poisoning are a major health problem accounting for significant morbidity and mortality worldwide [1]. The etiological profile of cholinesterase inhibitors poisoning varies in different world regions. In developing countries, where there is a lack of regulation and surveillance, inadequate protective equipment, and a large sector of agricultural industry, the incidences are expected to be higher. In some countries, such as China and Sri Lanka, self-poisoning with pesticides is a particularly severe problem [2-4].

The main circumstances of poisoning are suicide, homicide, accidental and occupational exposure. Since occupational and accidental poisoning requires a specific prevention and control measures, and suicidal exposures need a specific attention and predisposing factors assessment, it is important to accurately determine the magnitude of the problem through better estimates of cases and deaths resulting from cholinesterase inhibitors toxicity.

Although extensive data is available regarding the pattern of pesticide poisoning in many areas of the world,

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the data regarding the epidemiology of poisoning in an EU region (Northeastern part of Romania) is very scarce.

This study is aimed to assess the pattern and outcome of acute cholinesterase inhibitors poisoning cases in a tertiary care hospital in Iasi County, Romania and to identify where problems exist in order to stimulate better preventive and management strategies.

This study represents the first report of the pesticide poisoning cases referred to our hospital, which is the tertiary centre for the Northeastern region of Romania.

## 2 Materials and methods

This study retrospectively reviews all the acute CIS poisonings cases admitted to our hospital from January 1983 to December 2013. The information was obtained from medical hospital records. The selection of cases was based on the patient's diagnosis at discharge and decreased level of plasma butyrylcholinesterase (normal value 5-11 u/ml) through analyzing all the medical records of the patients hospitalized in our Internal Medicine and Toxicology Department. Physicians participating in the study abstracted all the data from the medical records. Data include patient's demographics (age, gender, occupation, residence), type and routes of exposure, clinical presentation, clinical forms of poisoning (mild, moderate, severe) according to W.H.O. classification of severity, history of psychiatric disease, associated alcohol intake, factors responsible for poisoning, plasma cholinesterase on admission, gastric lavage, the time between the exposure and hospital presentation, as well as clinical outcome. When the information was not available, it was classified as unknown.

Patients who did not require admission to the toxicology department and were discharged from the emergency unit were not included in this study.

The data were analyzed using SPSS for Windows 19.0. For nominal variables, the chi-square test was used for comparing variables for significant differences and the contingency coefficient was used as a measure of association. For numeric variables, means were compared using one-way ANOVA, followed by Bonferroni post hoc test. Differences were considered statistically significant for  $p$  values under 0.05.

**Ethical approval:** The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by

the authors' institutional review board or equivalent committee.

## 3 Results

A total number of six hundred and six patients were included, counting for 11% from the total number of acute poisonings. We summarize the results in the Table 1 for the easier comparison.

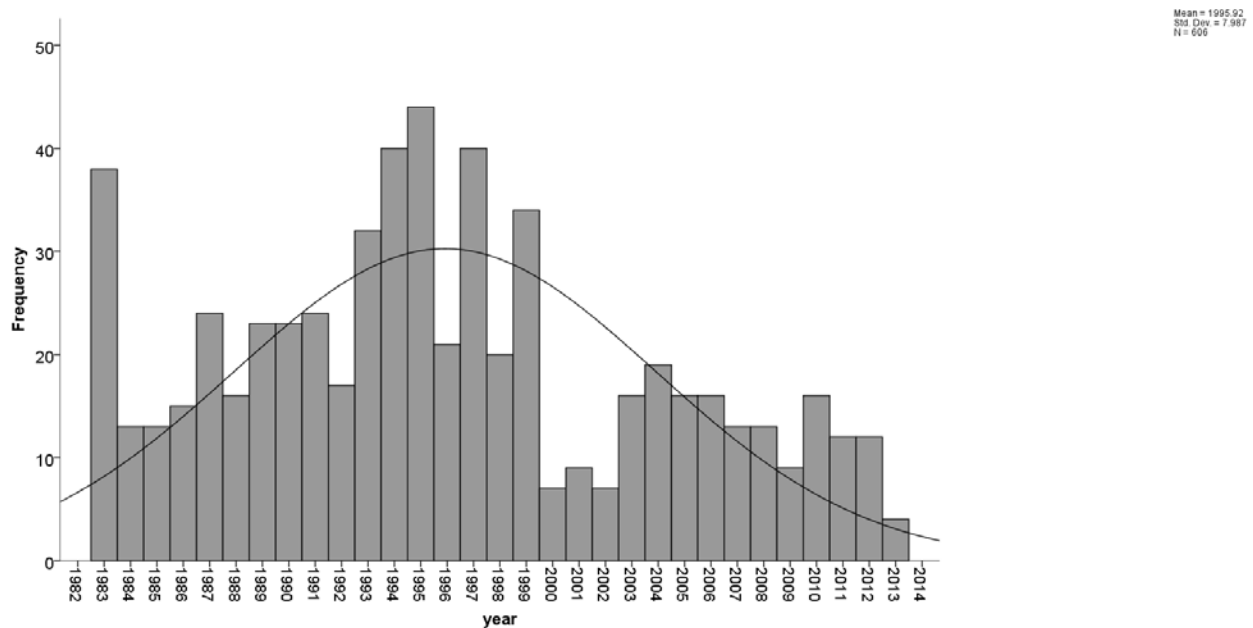
The highest numbers of cholinesterase inhibitors poisoning cases were hospitalized in 1995 (44 cases). Distribution of the cases number per year is observed in Figure 1.

From the total number of cases, 342 (56.4%) were females and 264 (43.6%) were males. The highest percent of cases (25.4%) were from the age group 20-29, followed by 30-39 (20.8%) (Figure 2). Most of the cases came from rural areas (404 – 66.7%), 28.2% being agricultural workers. The most common route of poisoning was oral (92.2%), only 2.5% dermal exposures and 2.1% inhalation. The reason for exposures was intentional in 70% of cases and accidental in 30%. In a majority of cases (90.1%) the cholinesterase inhibitors agent were unknown. In 5.6% of cases poisoning was a result of an association of toxic, pesticide and drugs, predominant sedative-hypnotics. Alcohol intake was associated in 38.6% of cases. The mean volume of CIS solution that was ingested was 77.40 ml. The amount ingested was bigger in male patients (90.10 ml) than in female patients (68.69 ml) ( $p < 0.004$ ). Previous psychiatric disorders were reported in 4.3% of the cases while 5.8% patients had a history of suicide attempt.

According to W.H.O. classification for severity of pesticide poisoning, 47% of cases were moderate and 36.6% were severe. Among severe clinical forms 55.9% of patients were female, predominant from 30-39 age group (23%), followed by 20-29 age group (20.7%). Among clinical forms, the mild forms were in almost equal percentage accidental (53.5%) or suicidal (43.4%). Moderate and severe forms were predominantly suicidal (70.5% and 81.1%). Severe forms were associated in 31.1% of cases with chronic alcoholism, the percentage being reduced in cases of mild (8.1%) or moderate forms (10.5%). 52.3% of patients presenting with severe signs and symptoms were associated with alcohol intake. Severe forms were accompanied by a more increased quantity of pesticide agent ingested compared with mild and moderate forms ( $p < 0.004$ ) and with more decreased serum cholinesterase on admittance ( $p < 10^{-4}$ ).

**Table 1:** Summary of results of the retrospective study

Features	No. of Patients	Percent
Total No. of Patients	606	100
Sex		
Females	342	56.4
Males	264	43.6
Residence		
Rural areas	404	66.7
Urban areas	202	33.3
Occupation		
Agricultural workers	171	28.2
Non-agricultural workers	435	71.8
Reason for exposures		
Intentional	424	70
Accidental	182	30
Route of poisoning		
Oral	559	92.2
Dermal exposure	15	2.5
Inhalational	13	2.1
Mixt	19	3.2
Cholinesterase inhibitor substances (CIS)		
Unknown	546	90.1
Known (Neocidol, Detox, Sineparatox, Diazole, Neguvon, Parathion, Other CIA)	60	9.9
Association of other toxic substances		
Alcohol intake	234	38.6
Drugs (Sedative-hypnotics)	34	5.6
Other substances	11	1.8
Medical history		
No medical history	370	61
Previous suicide attempt	35	5.8
Psychiatric disorders	26	4.3
Other comorbidities	175	28.9
Clinical forms		
Severe	222	36.6
Moderate	285	47
Mild	99	16.4
Outcome		
Discharged with medical recommendations	484	79.8
Discharged on request	64	10.6
Deceased	23	3.8
Ran out of hospital	20	3.3
Transferred	15	2.5

**Figure 1:** Distribution of the cases number per year.

Clinical features of cholinesterase inhibitors poisoning are presented in Table 2. The most common sign or symptom was nausea encountered in 73.1% of cases, followed by sweating (71.8) and bronchial hypersecretion (71.3%).

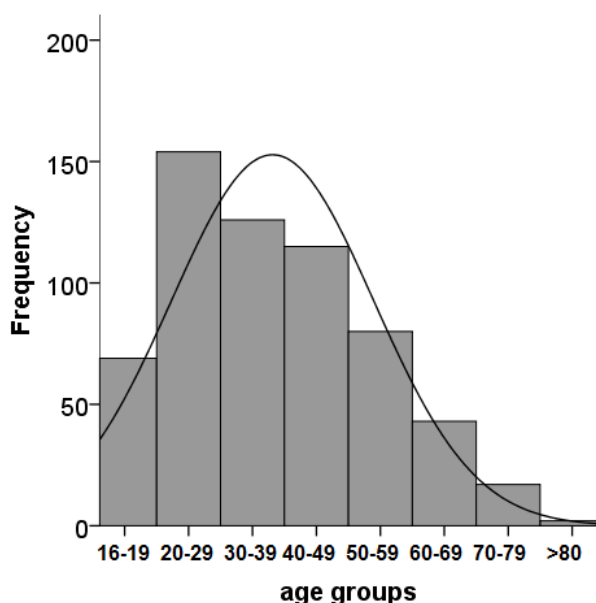
Possible factors responsible for poisoning were affective in 32.5% of cases and chronic alcoholism in 17.7%. The rest were either undeclared or an association of factors.

Plasma cholinesterase on admittance had a mean value of 1.5 u/ml. The minimum value of serum cholinesterase was registered in the age group of  $\geq 80$ , followed by 60-69 ( $p < 10^{-4}$ ) but without significant differences between genders ( $p$  0.084). Serum cholinesterase mean values on admittance were more decreased in severe forms (1.0 u/

ml) compared with mild (2.8 u/ml) and moderate forms (1.6 u/ml) ( $p < 10^{-4}$ ).

Gastric lavage was performed in 54.6 % (84%) of patients. The time interval between the poisoning moment and the hospital presentation was in average 8.78 hours. The increased value of standard deviation indicates the higher variability of the parameter in our group. Females arrived at the hospital 7.71 hours after poisoning and males 10.22 hours after the exposure, but the difference was not statistically significant ( $p$  0.41). Complications occurred in 9.4% of cases, especially acute pulmonary edema and toxic myocarditis. In the majority of cases the patients were discharged with a medical prescription (79.9%). Cases of release on request were registered (10.6%), before the finish of the entire medical act, against the doctor recommendations and warnings about possible complications. Only 2.5% of the patients were transferred towards psychiatry for specific measures.

Overall mortality rates were 3.8%. From the total number of deaths (23 cases) 82.6% were suicidal poisonings and only 17.4% accidental. More than half of the dead patients (65.2%) were associated with alcohol intake. Disorders of consciousness were the most common sign (73.9%) of presentation among the patient that died. It was a significant statistical association between the decrease of serum cholinesterase level on admittance and deaths ( $p < 10^{-4}$ ).



**Figure 2:** Distribution of the cases number in age groups.

## 4 Discussion

Our research provides the first comprehensive analysis of the cholinesterase inhibitors poisoning in this region. The analyzed data indicate that CIS exposures represent only 11% of the total number of hospitalized poisoning. Intentional pesticide poisoning exposure accounts for most of the poisoning cases. A retrospective study from

**Table 2:** Clinical Features of Organophosphorus Poisoning

Clinical Features	Yes		No		Unknown	
	No. of Patients	Percent	No. of Patients	Percent	No. of Patients	Percent
Sweating	435	71.8	171	28.2	0	0
Miosis	356	58.7	250	41.3	0	0
Nausea	443	73.1	163	26.9	0	0
Sphincter Relaxation	109	18.0	496	81.8	1	0.2
Fasciculation	300	49.4	306	50.5	0	0
Bradycardia	81	13.4	525	86.6	0	0
Disorders of Consciousness	166	27.4	440	72.6	0	0
Bronchial Hypersecretion	432	71.3	174	28.7	0	0

China with a total of 20097 pesticide poisoning cases showed that suicide was the most common reason for poisoning [3]. Other similar data come from Sri Lanka, India, South Korea and Nepal [4-8]. An article which has systematically reviewed the worldwide literature to estimate the number of pesticide suicides in each of the World Health Organisation's six regions concluded that pesticide self-poisoning is one of the most commonly used methods of suicide worldwide, and it accounts for about one-third of the world's suicides [9]. In developed countries such as United States and Sweden accidental poisoning is the leading cause of pesticide-related hospital admission [10,11].

We find that most of the cases were from rural areas but only 28.2% were agricultural workers. These data suggest a far too easy pesticide access for people without training or license use and improper storage facility.

The present study reveals the predominance of females with overall male to female ratio 1:1.29. In other studies male predominance has been reported [7,12-14]. This may be explained by non-occupational type of poisoning.

Almost half of the cases were young patients (aged 20-39) with a peak at 20-29 years of age. This pattern is similar with that reported from different other developing countries such as Costa Rica and India [15,16]. A different profile result from a survey from South Korea [7]. In this research, pesticide-related hospitalization increased with age, with the highest rate noted among those aged 70 or above. China and Japan have the same high suicide rate by pesticide poisoning in elderly people, compared with that in young and middle-aged adults [3,17]. The major limitation of our study is that we only included pesticide poisoning in adults aged over 16. Actually, children are an important group for self-harm through pesticides in some regions. Data from Minnesota, North and South Carolina and Milan, Italy showed that the mean age of all reported instances of pesticide poisoning (adults and children) was 5 years [18].

The most common clinical finding in our study was nausea followed by sweating and bronchial hypersecretion. Comparison of the clinical features observed in the present study with other studies showed that nausea is the most common symptom in all the studies, but bradycardia and miosis were more often encountered in other studies [19-21].

We have to note the concomitant use of alcohol in many patients, fact also reported in our study regarding drug poisoning, meaning that efforts to reduce self-poisoning may benefit from concurrent efforts to reduce alcohol consumption [22]. Associated alcohol use is also reported

in Sri Lanka [23]. The community efforts to reduce alcohol use produce additional major public health benefits. The authors pointed out that such attempt requires immense political will and it is difficult in Sri Lanka because of the political power of the alcohol industry and widespread illicit distilling of alcohol. The latter situation is also encountered in our country.

A small percentage of patients had history of psychiatric disorders; however an important reason for attempted suicide was affective disorders. Also not too many patients were transferred towards psychiatry. In literature most cases had a history of mental illness mostly depression followed by personality disorder as documented in almost all the studies reviewed by Risal *et al.* [24] Similarly, marital disharmony, family conflicts, economic hardships and family disputes were the major precipitating factors for the act in almost all the studies keeping with the findings in the Risal study [24-26]. We believe that in our country it is necessary to develop a better cooperation, based on a specified protocol, with the psychiatry department. Psychiatric care is essential for these patients in preventing future suicide attempts.

Severe forms are correlated in the present study with intentional poisoning, an increased amount of CIS and decreased level of cholinesterase. The reason of having butyrylcholinesterase as main specific test for cholinesterase inhibitors substances poisoning relates to the fact that in Romania, due to accessibility reasons, this was the most frequently used test. Also, plasma cholinesterase is easier to assay and is more readily available. Acetylcholinesterase tests even more sensible are also not so much used in daily clinical activity. The usefulness of butyrylcholinesterase (BuChE) activity measurement on admission to stratify severity in acute insecticide poisoning has been debated for long. Some studies showed that plasma BuChE activity on admission can provide useful information but it must be interpreted critically with definite knowledge of the ingested CIS [27]. Overall, a BuChE activity on admission is only useful when the CIS pesticide has been identified and when its sensitivity and specificity is known for that particular pesticide. Our data had lack of information about the specific CIS involved but we find a statistically significant correlation between severe forms, death and decreased serum BuChE on admittance.

In our study the patients came late to the hospital, in average 8.78 hours, however the gastric lavage was performed in more than half of the patients. Gastrointestinal decontamination with gastric lavage is now used less often in the hospital setting because there is currently no high-quality evidence to support its clinical effectiveness in pesticide poisoning [28]. Additionally, the importance



of iatrogenic deaths caused by inappropriate gastric decontamination as shown by the number of deaths occurring after ingestion of low toxicity pesticides needs to be emphasized [29]. Despite extensive evidence demonstrating little benefit and significant risk of gastric lavage in the management of poisoned patients, it is still extensively used in Romania, like in other region from Asia [28,30]. We consider this decontamination method still useful based on its simple technique, reduced cost and effectiveness in the first hours post ingestion with respect for all well known possible complications, that can be minimized by a trained personnel.

Overall mortality rates were 3.8%. The majority of the cases were suicidal poisonings, presenting with disorders of consciousness, decreased level of serum cholinesterase on admittance and more than half of the deceased patients were having associated alcohol intake. This decreased mortality rate was described in epidemiological studies accomplished in India and Morocco [5,31]. Other studies from South Korea and Taiwan reported increased mortality probably in relation with utilization of WHO Pesticide Hazard Class I OPs [7,32]. Alcohol co-ingestion is known to be associated with higher plasma concentrations of some CIS and increased risk of death [33]. Also decreased concentrations of plasma cholinesterase was considered a factor for increased mortality in a previous prospective case series study [34].

## 5 Conclusions

The pattern of poisoning described by our study suggests that CIS poisoning is mainly preventable. One strategy to reduce these poisoning cases is to restrict the availability and accessibility of toxic pesticides, adopting a non-pesticide management policy. The second approach is to improve educational measures regarding the danger of pesticide poisoning and safekeeping of pesticides. Another measure is to encourage manufacturers to improve the safety of their products by diluting the concentrations of liquid pesticides, incorporating emetics or, more fundamentally, to produce pesticides which are non-toxic to humans.

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**Conflict of interest:** Authors state no conflict of interest

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