PRELIMINARY REPORT

https://doi.org/10.23873/2074-0506-2024-16-1-54-63

Analysis of fatal outcome structure in acute poisoning with hypotensive and antiarrhythmic drugs

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Abstract

***Background**. In many countries, there is an increase in the number of poisoning with antihypertensive and antiarrhythmic drugs taken either accidentally or for suicidal purposes. The mortality rate for these poisonings reaches 6.5%.*

The aim of the study was to analyze the causes of fatal outcomes in patients with acute poisoning with hypotensive and antiarrhythmic drugs.

***Material and methods**. The inpatient medical records (Form No. 003/y), autopsy reports of forensic chemical and forensic histological studies of 80 people who died from acute poisoning with hypotensive and antiarrhythmic drugs at the N.V. Sklifosovsky Research Institute for Emergency Medicine for the period from 2011 to 2020 were analyzed.*

***Results.** The age of patients with acute poisoning with antihypertensive and antiarrhythmic drugs ranged from 16 to 94 years, of which 85% of patients were over 60 years old. Women made up 70%. Twenty five patients died in the toxicogenic stage of poisoning, other 55 died in the somatogenic stage. The causes of poisoning were the intake of hypotensive drugs (mainly calcium channel blockers) in 67% of cases, the intake of antiarrhythmic drugs from the group of beta-blockers in 33%. Poisoning on suicidal intent was recorded in 81.2% of cases. The main causes of death in the toxicogenic stage of poisoning were the following (listed in order of decreasing incidence): exotoxic shock, primary cardiotoxic effect, acute cardiovascular insufficiency. The main cause of patient death in the somatogenic stage was pneumonia.*

***Conclusion.** Acute poisoning with antihypertensive and antiarrhythmic drugs, in the vast majority of cases, occurs in patients over 60 years of age. Suicidal attempts make the main cause of poisoning. The main cause of death in the toxicogenic stage of poisoning is exotoxic shock, that one in the somatogenic stage is nosocomial pneumonia.*

Keywords: antihypertensive and antiarrhythmic drugs, acute poisoning, exotoxic shock, pneumonia, death, suicide

Conflict of interest. The authors declare no conflict of interest

Financing The study was performed without external funding

For citation: Ilyashenko KK, Sukhodolova GN, Belova MV, Simonova AYu, Potskhveriya MM. Analysis of fatal outcome structure in acute poisoning with hypotensive and antiarrhythmic drugs. *Transplantologiya. The Russian Journal of Transplantation.* 2024;16(1):54–63. (In Russ.). https://doi.org/10.23873/2074-0506-2024-16-1-54-63

AADs, antiarrhythmic drugs
ACE, angiotensin-converting enzyme
ACVF, acute cardiovascular failure
AHDs, antihypertensive drugs
ARF, acute renal failure
CNS, central nervous system
CVA, cerebrovascular accident
PCE, primary cardiotoxic effect
PE, pulmonary embolism

Introduction

Acute diseases of chemical etiology in the Russian Federation remain a serious medical and social problem due to their periodic incidence, fairly high level of deaths, and frequent disability [1, 2].

Despite the changes that occurred at the beginning of the 21st century in the general structure of acute exotoxicoses, drug poisoning still occupies the leading place [3, 4]. Among the drugs causing poisoning, from 7.8% to 9.4% are the drugs acting on the cardiovascular system, including β-blockers, angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, and AT_1 receptor antagonists [5–7]. In our opinion, this is primarily due to a wide prevalence and growth of cardiovascular system diseases [8] and the use of these substances for medicinal purposes. We should note that many drugs of these classes are included in the List of Vital and Essential Medicines [9]; and are over-the-counter drugs sold in pharmacies without doctor's prescription, which increases their availability to the population and, accordingly, increases the risk of poisoning. Mortality reaches 6.5% [10].

The objective was to analyze the structure of deaths in acute poisoning with antihypertensive and antiarrhythmic drugs.

Material and methods

The study material was inpatient medical records (Form No. 003/u) and autopsy reports of forensic chemical and forensic histological studies of 80 patients died from acute poisoning with antihypertensive drugs (AHDs) and antiarrhythmic drugs (AADs) at the N.V. Sklifosovsky Research Institute for Emergency Medicine in the period from 2011 to 2020. The antiarrhythmic drugs, which accounted for 33% of the studied toxicants, were atenolol, propranolol, bisoprolol, and metaprolol. Among the drugs that have antihypertensive effect, 15% of the total were ACE inhibitors (enalapril, captopril, perindopril), and in 52% of cases they were calcium channel blockers (nifedipine, amlodipine, felodipine, verapamil). The presence of these drugs in the biological media (urine) of patients was confirmed by chemical and toxicological assays performed on patient admission at the hospital. Toxicants were identified after their extraction from urine using gas-liquid chromatography–mass spectrometry using an *Agilent* 7890 *B* device with *a 5977 B* mass selective detector. Statistical analysis of the data was made using a Computer Microsoft software package Office Excel.

Results and discussion

The fatal outcome in 25 patients who died within the first 3 days took place at toxicogenic stage of poisoning. This was confirmed by the detection of study drugs in the urine of patients during that period; in the remaining patients, death occurred in the somatogenic stage of poisoning. We considered it appropriate to analyze deaths in each of these groups.

In table 1 presents the characteristics of patients who died in the toxicogenic stage of poisoning.

Table 1. Distribution of patients who died in the toxicogenic stage of poisoning, by age, gender and causes of poisoning

Drug group	Patient age							
	Under 60 years old; n=4				60 years and older; n=21			
	Accidental		Suicidal intent		Accidental		Suicidal intent	
	m	f	m	f	m	f	m	f
AADs	-	-	-	1	1	3	4	2
AHDs	-	-	1	2	1	2	2	6

Table 1 shows that the majority of those who died during the first 3 days after hospital admission were the patients of the older age group: the mean patient age in the group was 70.7±2.8 years old; there were 16 (64%) women and 9 (36%) men. In 18 patients (72%), death occurred within the first day after admission at the hospital. The period from the moment of taking the toxicant to hospital admission ranged from 3 to 6 hours for most of the victims, and from 10 to 14 hours in 5 cases. In 18 patients (72%), poisoning occurred as a result of suicide, while in 7 elderly people (28%) it was accidental.

In the group of patients who took AADs, the use of bisoprolol predominated; and among those who took AHDs, calcium channel blockers were predominantly used. In 3 cases of poisoning with β-blockers, alcohol was also found in the biological media of patients in concentrations: from 0.76 g/L to 1.27 g/L in blood, and from 0.37 g/L to 3.2 g/L in urine. With this combination, as is known, the antihypertensive effect of β-blockers is enhanced and the inhibitory effect of ethanol on the central nervous system (CNS) is more pronounced [11]. In 11 cases (44%) a single-drug poisoning was

reported. Five patients (20%) took antihypertensive drugs in combination with beta-blockers, and three patients took them in combination with digoxin.

According to the literature, with sequential or simultaneous administration of drugs that act on the cardiovascular system, their synergy can be observed: an increased effect of one toxicant under the effect of another; the degree of synergy can be determined by the simple sum of the effects of each of them or by their mutual potentiation [12–14].

In 6 patients (24%) a combination of AAPs and AHPs with the psychopharmacological drugs was found in the biological media; there were identified phenazepam, phenobarbital, chlorprothixene, carbamazepine among them.

Table 2 provides information on patients with AAP and AHP poisoning who died at somatogenic stage of poisoning.

Table 2. Distribution of patients who died in the somatogenic stage of poisoning, by age, gender and causes of poisoning (n=55)

Drugs	Patient age							
	Under 60 years old; n=8				60 years and older; n=47			
	Accidental		Suicidal intent		Accidental		Suicidal intent	
	m	f	m	f	m	f	m	f
AADs	-	-	-	1	2	1	1	12
AHDs	-	-	4	3	4	1	4	22

The data in Table 2 demonstrate that among those who died at somatogenic stage of poisoning there were 72.7 % women and 27.3 % men. Just as in the previously mentioned group, patients over 60 years of age were in the majority (n=47; 85.5%). In all patients under the age of 60, the cause of poisoning was a suicide. In the older age group, suicidal tendencies were confirmed in 83% of patients. In 17% of cases, poisoning

occurred as a result of an accidental overdose of drugs, as a rule, when they were used in combination with other drugs (erroneous use, self-medication).

It has been noted that cardiovascular diseases more often affect elderly people, in whom, due to age-related characteristics of the body, the pharmacodynamics and pharmacokinetic parameters of drugs change, which is accompanied by poisoning symptoms more often than in young people. In addition, older patients often violate the dosage and frequency of taking medications, which are the frequent causes of poisoning [11–13].

Seven patients of working age took AHDs (enalapril and/or amlodipine), and one patient took bisoprolol. Among patients over 60 years of age, the use of AHDs (ACE inhibitors and calcium channel blockers) was recorded in 69% of cases, AADs in 31%.

Twenty two people (40%) took drugs of the same name; a combined use of AHD and AAP occurred in 17 patients (31%). In two cases, the use of ACE inhibitors and digoxin was recorded. In 16 patients (2%), a combination intake with psychopharmacological drugs was detected, including barbituric acid derivatives, phenothiazine derivatives, chlorprothixene, and carbamazepine.

A number of authors have noted that a combination use of β-blockers with antipsychotics can enhance the inhibitory effect of the latter on the central nervous system and is accompanied by a more pronounced hypotensive effect [13, 15, 16].

Table 3 presents complications that develop in patients at toxicogenic stage of AAD and AHD poisoning.

Table 3. Complications of the toxicogenic stage of acute poisoning with antihypertensive and antiarrhythmic drugs in patients under and over 60 years of age (n=25)

Complications	Under 60 years old, n=4		Incidence, %	60 years and older, n=21		Incidence, %	Total incidence, %
	AADs	AHDs		AADs	AHDs		
Pneumonia	–	–	0	–	3	14.3	12
PATE	–	–	0	–	2	9.5	8
Purulent tracheobronchitis	–	–	0	–	3	14.3	12
Non-occlusive thrombosis and necrosis of the small intestine mucosa	–	–	0	1	1	9.5	8
Exotoxic shock	2	2	100	4	5	42.9	52
Primary cardiotoxic effect	2	–	50	6	2	38.1	40
Acute cardiovascular failure	2	1	75	1	1	9.5	20

Note: PATE, pulmonary artery thromboembolism

Table 3 shows that the most common complication of acute poisoning with AADs and AHDs in people who died in the first 3 days of hospital admission was exotoxic shock accounting to 52%, of which 36% of patients were over 60 years old. Among people under 60 years of age, exotoxic shock was recorded in all deaths. Shock was recorded in 28% of cases in poisoning with AHD, and in 24% in poisoning with β-blockers. The development of exotoxic shock as a complication of poisoning with antiarrhythmic drugs was also noted by other researchers [17].

The second most common complication was a primary cardiotoxic effect accounting for 40% of cases, mainly in poisoning with β-blockers. It was recorded in 2 patients under 60 years of age, and in 8 elderly and senile patients. Acute cardiovascular failure ranked third in incidence

(20%). In some cases, a combination of exotoxic shock and a primary cardiotoxic effect was noted, mainly in gerontological patients.

Pneumonia in combination with purulent tracheobronchitis ranked the next by incidence (12% each). Such complications were not observed among young people. At the same time, inflammatory infiltrates in the lungs were detected in 2 gerontological patients upon hospital admission, and in one case one day after hospital admission. In some solitary cases of older people, there were pulmonary embolism and non-occlusive thrombosis and necrosis of the small intestine mucosa.

Complications in patients who died at somatogenic stage of poisoning are presented in Table. 4.

Table 4. Complications of the somatogenic stage of acute poisoning with antihypertensive and antiarrhythmic drugs (n=55)

Complications	Under 60 years old, n=8		Incidence, %	60 years and older, n=47		Incidence, %	Total incidence, %
	AADs	AHDs		AADs	AHDs		
Pneumonia	2	5	87.5	18	24	89.4	89.1
Thrombosis	2	3	62.5	2	5	14.9	21.8
Acute myocardial infarction	–	–	–	12	1	27.7	23.6
PATE	1	2	37.5	2	2	8.5	12.7
Gastrointestinal bleeding	–	3	37.5	–	1	2.1	7.3
Hydrothorax	1	3	50	4	9	27.6	30.9
Purulent tracheobronchitis	1	1	25	3	16	40.4	38.2
Epiglottis paresis	–	–	0	–	1	2.1	1.8
CVA	–	–	0	2	5	14.9	12.7
ARF	–	–	0	–	3	6.4	5.4
Stomach wall perforation, peritonitis	–	–	0	–	1	2.1	1.8
PCE	–	1	12.5	1	3	8.5	9.1

Notes: CVA, cerebrovascular accident; ARF, acute renal failure; PCE, primary cardiotoxic effect

In patients who died at somatogenic stage of poisoning (Table 4), the leading complication was pneumonia, which was diagnosed in 52.7% of AHD poisoning cases. The incidence of this complication did not differ statistically significantly between the age groups studied. Its duration in 2 patients under 60 years of age with AAD poisoning was 14 calendar days (c/d), and 5.5±0.7 c/d for those with AHD poisoning. Patients in the older age group died from this complication due to AP and GP poisoning after 14.1±4.5 and 21.4±2.9 days of hospital stay, respectively. Purulent tracheobronchitis was accompanied by pneumonia in 38.2% of cases. Hydrothorax was identified in patients with developed acute renal failure and severe bilateral polysegmental pneumonia, being caused by protein loss in presence of severe endotoxicosis.

Complications of vascular nature (lower limb venous thrombosis, myocardial infarction, stroke, pulmonary embolism) were mostly diagnosed in patients over 60 years old, in the period from 6 to 25 days. In the pathogenesis of these complications, the initially compromised vessels of the victims were of great importance. Electrocardiographic signs of PCE persisted in patients up to 3 days of hospital stay, mainly in those who died from poisoning with calcium channel blockers.

The causes of death in patients with acute AHD and AAD poisoning are presented in Table. 5 for those died at toxicogenic stage, and in Table 6 for those dies at somatogenic stage.

Table 5. Causes of patients' death in the toxicogenic stage of poisoning with antihypertensive and antiarrhythmic drugs

Causes of death	Patient age			
	Under 60 years old, n=4		60 years and older, n=21	
	AADs	AHDs	AADs	AHDs
Exotoxic shock	2	2	4	5
Acute cardiovascular failure	2	1	1	1
PATE	–	1	1	3
Myocardial infarction	–	–	–	2

Table 5 shows that exotoxic shock was the leading cause of death at toxicogenic stage of acute poisoning with AADs and AHDs. Noteworthy is the 4-fold increase in the number of patients who died from pulmonary embolism in the older age group.

Table 6. Causes of patients' death in the somatogenic stage of poisoning with antihypertensive and antiarrhythmic drugs (n=55)

Causes of death	Patient age			
	Under 60 years old, n=8		60 years and older, n=47	
	AADs	AHDs	AADs	AHDs
Pneumonia	1	6	9	27
Acute myocardial infarction	–	–	1	1
CVA	–	–	1	2
ACVF	–	–	2	2
PATE	–	1	–	–
Multiple organ failure	–	–	–	2

Note: ACVF, acute cardiovascular failure

As can be seen from Table 6, nosocomial pneumonia was the main cause of death in the patients with antihypertensive and antiarrhythmic drugs at somatogenic stage of acute poisoning.

Conclusion

The studies undertake have shown that acute poisoning with antihypertensive and antiarrhythmic drugs is overwhelmingly seen in patients over 60 years of age. The main cause of poisoning is suicide attempts. The main cause of death is exotoxic shock in the toxicogenic stage of poisoning, and nosocomial pneumonia in the somatogenic stage of poisoning.

Thus, we may make the following conclusions:

1. In the poisoning cases studied, death from poisoning with antiarrhythmic drugs occurred in 33% of patients, and that from poisoning with antihypertensive drugs was recorded in 67% of cases. Patients over 60 years old accounted for 85% of the total number of deaths. In 70% of cases, poisoning was reported in women. Poisoning was suicidal by nature in 81.25% of patients.

2. The most common complications at toxicogenic stage of acute poisoning with antiarrhythmic and antihypertensive drugs include: exotoxic shock (52%), primary cardiotoxic effect (40%), acute cardiovascular failure (20%), and those at somatogenic stage of poisoning were pneumonia (89, 1%), purulent tracheobronchitis (38.2%)), hydrothorax (30.9%), venous thromboembolic complications (21.8%).

3. The main causes of death in patients with acute poisoning with antiarrhythmic and antihypertensive drugs are exotoxic shock accounting for 16.3% and pneumonia making 53.8% of all cases examined.

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The article was received on July 7, 2023;
approved after reviewing July 26, 2023;
accepted for publication December 27, 2023