

# CARDIOVASCULAR DISORDERS IN ACUTE DRUG INTOXICATIONS: SIX YEARS EXPERIENCE OF A TERTIARY POISON CENTER FROM ROMANIA

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## ABSTRACT

**Objective.** To analyze the pattern of dysrhythmias and arterial blood pressure changes occurring in acute drug intoxications.

**Method.** Retrospective study concerning medical records from six years, regarding patients from Toxicology Clinic of Emergency Hospital of Iasi, Romania, admitted for acute drug poisoning. Arterial blood pressure values and patterns of abnormal electrocardiogram occurring in the first 6 hours after admission were analyzed.

**Results.** 695 cases of acute drug poisonings were analyzed. Hypertension was encountered in 6.6%, and hypotension was observed in 14.1% of the patients. Hypotension occurred in a significant percent in cardiovascular drugs (48.6%) and barbiturates poisonings (25.8%). Tachycardia was documented in 26.5% of the patients, bradycardia being found in 8.3% of the cases. Tachycardia was frequently associated with polimedication (36.8%), benzodiazepines (12.6%) followed by anticonvulsants (8.2%) and barbiturates (7.7%). Bradycardia was documented in 30.4% of the polimedication poisoning cases, 17.9% of barbiturates, 16.1% of cardiovascular drugs and 8.9% of the benzodiazepine poisoning cases. Only 14.8 % of the patients have rhythm and conduction disturbances other than tachycardia or bradycardia. On electrocardiogram, the most frequent finding was ischemia, followed by conduction abnormalities. Supraventricular arrhythmia was rarely encountered, in only 12 cases while ventricular arrhythmia was even rarest (one case of ventricular tachycardia).

**Conclusion:** Cardiac toxic effects were rare in acute drug poisonings cases admitted in our clinic, manifested especially as moderate clinical forms and drug-induced coma. The study did not reveal any life-threatening or cases of deaths.

**Keywords:** dysrhythmias, epidemiology, poisonings, drug toxicity

## INTRODUCTION

Acute poisonings continue to represent an important cause of morbidity and mortality all around the world. According to the American Association of Poison Control Centers (AAPCC), drugs have the biggest incidence among poisonings, followed by household products (1).

When occurring in acute poisonings, cardiovascular complications, especially dysrhythmias, lead to poor outcomes, even death (2).

In the past, case reports and case series were the studies most commonly published in this respect. The lack of epidemiological information regarding

rhythm and conduction disturbances in acute drug poisonings determined us to conduct this study.

Our aim was to analyze the pattern of dysrhythmias and arterial blood pressure changes occurring in acute drug poisonings and to compare these data with similar reports from literature.

The study was performed on 695 cases of acute drug poisonings, admitted at the Internal Medicine Toxicology Clinic of Emergency Clinical Hospital Iasi, the place where all the poisoned patients from Iasi County are referred. It represents the tertiary center for Clinical Toxicology in the North-Eastern region of Romania.

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## METHODS

A retrospective analysis of medical records was performed for all 695 patients admitted with acute drug poisonings in The Toxicology Clinic of the Emergency Clinical Hospital Iasi, Romania, in the previous six years. The cases were selected based on the patient's diagnosis on discharge, by analyzing the medical records of all hospitalized patients. The charts were abstracted by physicians participating in the study using a standardized data collection form, in a Microsoft Excel spreadsheet.

The demographical data (age, gender) were collected, as well as additional parameters such as: drug category, clinical form of poisoning (mild, moderate, and coma), declared alcohol intake and blood alcohol levels. The values of the blood pressure were recorded and an analyze of the recordings of electrocardiographic changes in all patients in the first 6 hours was also performed. Electrocardiographic disturbances, hypo- or hypertension recorded before the actual hospitalization or declared by the patient, relatives or supported by previous medical documents, were not included.

Drugs were classified as benzodiazepines, barbiturates, neuroleptics, anticonvulsants, antidepressants, cardiovascular drugs, acetaminophen, NSAIDs and nonopioid analgesics, antibiotics, hypoglycemic agents, opioids, tuberculostatics, other medication (vitamins, antithyroid drugs, iron compounds, etc.) and unknown drugs.

First, the blood pressure changes were quantified and the patients were classified in three categories: normal blood pressure, hypertension (>140/90

mmHg in accordance with The European Society of Hypertension Guide 2013) and hypotension (<90/60 mmHg) (3).

Depending on the heart rate, patients were divided in three categories: normal heart rate, tachycardia and bradycardia.

Electrical changes were analyzed and grouped in the following categories: normal electrocardiogram, premature beats, ischemic changes, conduction disturbances, supraventricular arrhythmias, long QT interval, ventricular arrhythmias.

For the accuracy of the study, two teams of abstractors revised all the data, including electrocardiogram. Inter-rater reliability was calculated by using 36 (6 per year) medical charts. All abstractors reviewed the entire set of randomly selected medical charts. Inter-rater agreement was assessed by using  $\kappa$  analysis.

The database was statistically analyzed using SPSS for Windows 16.0. The chi-square test for comparing nominal variables was used when proportions were analyzed for significant differences (4). Differences were considered statistically significant when p values were under 0.05.

## RESULTS

For the given period of six years, 2556 cases of acute poisonings were recorded and drug poisonings weighted for 27.19% (695 cases).

The blood pressure was normal in 79.3% of patients, hypertension was encountered in 6.6% and in 14.1% of the patients hypotension was observed.

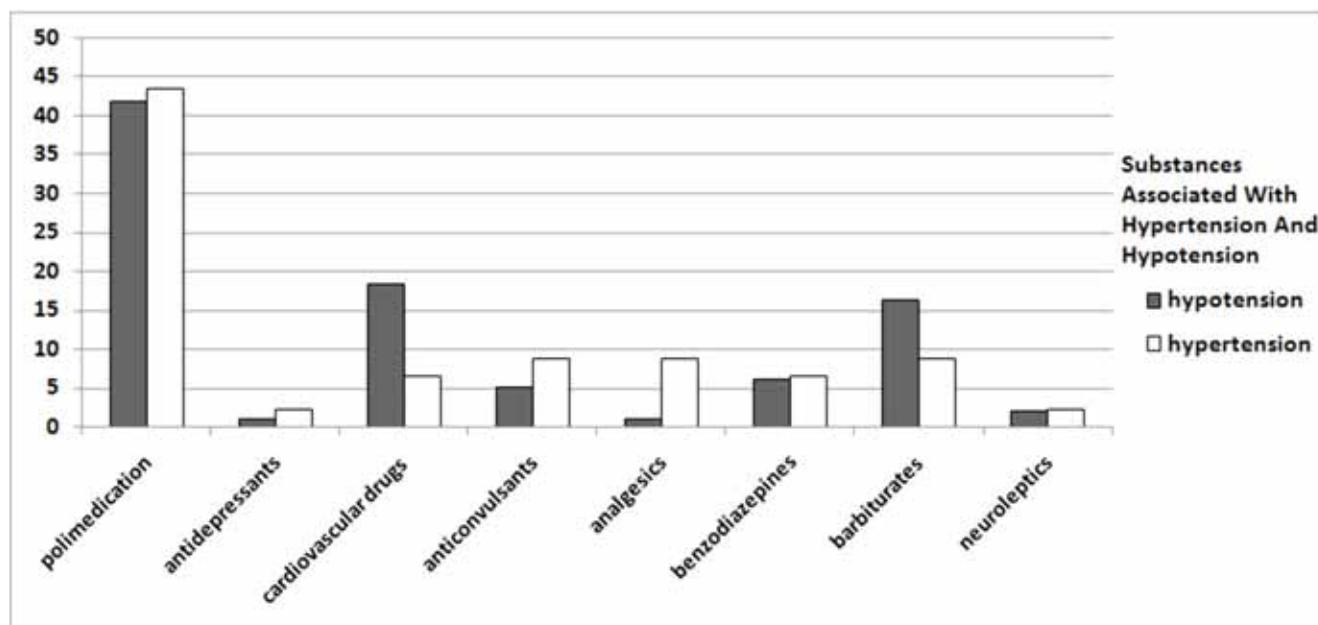


FIGURE 1. Substances associated with hypertension and hypotension

From the total number of hypertension cases, 43.5% of patients ingested more than one drug, 8.7% were barbiturates poisonings, 8.7% anticonvulsants and 8.7% were analgesics poisoning (p 0.000) (Figure 1).

Out of the total cases of hypotension, 41.8% were encountered in polimedication poisonings, 18.4% in cardiovascular drug poisonings and 16.3% in barbiturates poisonings (p 0.000) (Figure 1).

Analyzing the drug category responsible for the poisoning, we observed that hypotension occurred in a significant percent in cardiovascular drugs (48.6%) and barbiturates poisonings (25.8%) (Table 1).

In womens, we have registered 25 cases of hypertension and in men 21 cases. Hypotension occurred more frequently in women (67 cases) than men (31 cases) (p 0.000).

The highest number of hypertension cases was observed in patients aged 41-50 years, while hypotension was more frequent in the 21-30 age group (p 0.000).

Hypotension was more frequent in patients with concomitant use of alcohol (76.5%) comparing with patients without declared alcohol consumption (23.5%) (p 0.000).

From the total number of 46 hypertension cases, in 20 cases the blood alcohol level was over 50 mg/dl, in 14 cases was normal and in 12 cases the alco-

hol blood exam was not determined. For hypotension (98 cases), 18 cases were accompanied by blood alcohol level higher than 50 mg/dl, in 46 cases the level was normal and in 34 cases the alcoholemia was not determined (p 0.01).

Both arterial blood pressure changes (hyper- or hypotension) had an increased incidence in moderate and severe clinical forms (coma) when comparing to mild forms (p 0.000).

The heart rate had normal values in 65.2% of the patients, tachycardia in 26.5% and in 8.3% of cases bradycardia was encountered.

For heart rate disturbances there were no statistically significant differences between age and gender groups.

Out of the total number of tachycardia cases, 36.8% were associated with polimedication, 12.6% with benzodiazepines poisonings, followed by anticonvulsants (8.2%) and barbiturates poisonings (7.7%).

Bradycardia was encountered in 30.4% of the cases in polimedication poisonings, 17.9% in barbiturates, 16.1% in cardiovascular drugs and 8.9% in benzodiazepine poisoning cases.

In relation with drug category, we noticed that from the total number of benzodiazepine poisonings, 24% had tachycardia, the same situation (around 25% of the total number of patients) being encountered in neuroleptics, anticonvulsants, NSAIDs, non-opioid analgesics and tuberculostat-

**TABLE 1.** Characteristics of blood pressure and heart rate considering the drug category inducing the poisoning

| Category                        | TOTAL CASES (No.) | BLOOD PRESSURE |                  |                  | HEART RATE |                 |                 |
|---------------------------------|-------------------|----------------|------------------|------------------|------------|-----------------|-----------------|
|                                 |                   | NORMAL (%)     | HYPERTENSION (%) | HYPO-TENSION (%) | NORMAL (%) | TACHYCARDIA (%) | BRADYCARDIA (%) |
| POLIMEDICATION                  | 255               | 76.1           | 7.8              | 16.1             | 65.9       | 27.1            | 7.1             |
| DRUGS AND OTHER SUBSTANCES      | 10                | 90.0           | -                | 10.0             | 60.0       | 30.0            | 10.0            |
| BENZODIAZEPINES                 | 96                | 90.6           | 3.1              | 6.3              | 70.8       | 24.0            | 5.2             |
| BARBITURATES                    | 62                | 67.7           | 6.5              | 25.8             | 59.7       | 22.6            | 17.7            |
| ANTIDEPRESSANTS                 | 19                | 89.5           | 5.3              | 5.3              | 52.6       | 42.1            | 5.3             |
| NEUROLEPTICS                    | 25                | 88.0           | 4.0              | 8.0              | 76.0       | 24.0            | -               |
| CARDIOVASCULAR DRUGS            | 37                | 43.2           | 8.1              | 48.6             | 54.1       | 21.6            | 24.3            |
| ACETHAMINOPHEN                  | 10                | 90.0           | 10.0             | -                | 80.0       | 10.0            | 10.0            |
| ANTICONVULSANTS                 | 56                | 83.9           | 7.1              | 8.9              | 64.3       | 28.6            | 7.1             |
| NSAIDs and NONOPIOID ANALGESICS | 20                | 75.0           | 20.0             | 5.0              | 70.0       | 25.0            | 5.0             |
| ANTIBIOTICS                     | 5                 | 100.0          | -                | -                | 80.0       | 20.0            | 0               |
| HIYPOGLYCEMIC AGENTS            | 5                 | 100.0          | -                | -                | 100.0      | -               | -               |
| OPIOIDS                         | 2                 | 50.0           | -                | 50.0             | 50.0       | 50.0            | -               |
| TUBERCULOSTATICS                | 14                | 85.7           | -                | 14.3             | 64.3       | 28.6            | 7.1             |
| OTHERS                          | 29                | 96.6           | 3.4              | -                | 55.2       | 41.4            | 3.4             |
| UNKNOWN DRUGS                   | 50                | 84.0           | 8.0              | 8.0              | 64.0       | 26.0            | 10.0            |
| <b>TOTAL</b>                    | <b>695</b>        |                |                  |                  |            |                 |                 |

ics. Tachycardia was found in an important percent (42.1%) of all the antidepressants poisoning cases and in 17.7% in barbiturates poisonings (Table 1).

The incidence of tachycardia and bradycardia was almost the same in clinical forms of moderate severity or those in coma when compared to mild forms: 62 cases of tachycardia and 21 cases of bradycardia in mild forms, 52 cases of tachycardia and 23 cases of bradycardia in moderate forms and 68 cases of tachycardia and 12 cases of bradycardia in coma situations (p 0.000).

Tachycardia was more frequent in patients with declared alcohol intake (p 0.004). In six of the cases of bradycardia, the blood alcohol levels were between 50-300 mg/dl, in 25 cases the levels were normal and in 25 cases these tests were not demanded. For the majority of the tachycardia cases (76 cases) the blood alcohol levels were normal, in 48 cases the levels were between 50 and 300 mg/dl and in 58 cases testing were not recommended.

The distribution of combinations between heart rate disturbances and arterial blood pressure changes are illustrated in Table 2. The differences were statistically significant (p 0.000).

**TABLE 2.** The distribution of combinations between heart rate disturbances and arterial blood pressure changes

| HEART RATE  | ARTERIAL BLOOD PRESURE |              |             | Total Cases no |
|-------------|------------------------|--------------|-------------|----------------|
|             | Normal                 | Hypertension | Hypotension |                |
| Normal      | 393                    | 21           | 39          | 453            |
| Tachycardia | 129                    | 22           | 33          | 184            |
| Bradycardia | 29                     | 3            | 26          | 58             |
| Total       | 551                    | 46           | 98          | 695            |

Electrocardiogram, being a routine test, was performed in all patients with acute drug poisonings. Normal aspects of electrocardiogram were recorded in 85.2% of patients, and only 14.8% of the patients had rhythm and conduction disturbances other than tachycardia or bradycardia (Figure 2).

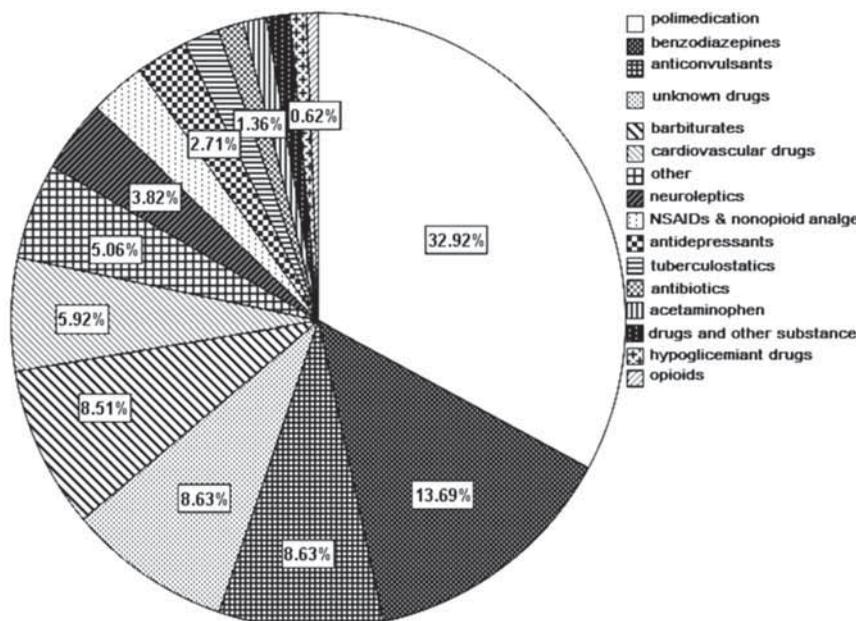
The most frequent finding on electrocardiogram was ischemia (40 cases) followed by conduction disturbances (35 cases) (Table 3). Supraventricular disturbances were a rarely encountered condition, found in only 12 cases, and just one case of ventricular arrhythmia was observed (ventricular tachycardia). The biggest number of abnormal electrocardiograms was found in cardio-vascular drug poisonings (12 cases) and benzodiazepine poisonings (9 cases) (p 0.003).

Patients aged 31-40 years associated the highest incidence of electrocardiogram disturbances (p 0.000).

The clinical forms of moderate severity and those of comatose patients associated more often electrocardiographic abnormalities (p 0.000). There were 32 cases of abnormal electrocardiogram in mild forms (8.86%), 33 in moderate forms (16.75%) and 36 cases in comatose status (26.27%).

There were no statistically significant differences between cases with declared alcohol intake as compared with cases without alcohol intake for abnormal electrocardiograms.

Electrocardiographic disturbances occurred more frequently in cases with tachycardia (38 cases) comparing with bradycardia (13 cases) (p 0.02) and in patients with hypotension (p 0.006).



**FIGURE 2**

**TABLE 3.** *Electrocardiogram recordings in acute drug poisonings in relation with drug category*

| CATEGORY                        | Normal<br>EKG | Premature<br>beats | Ischemia  | Conduction<br>disturbances | SVD       | VD       | LONG QT  |
|---------------------------------|---------------|--------------------|-----------|----------------------------|-----------|----------|----------|
| POLIMEDICATION                  | 204           | 3                  | 22        | 18                         | 6         | 1        | 1        |
| DRUGS AND OTHER SUBSTANCES      | 9             | -                  | -         | 1                          | -         | -        | -        |
| BENZODIAZEPINES                 | 87            | -                  | 5         | 3                          | -         | -        | 1        |
| BARBITURATES                    | 55            | -                  | 3         | 2                          | 1         | -        | 1        |
| ANTIDEPRESSANTS                 | 18            | -                  | -         | 1                          | -         | -        | -        |
| NEUROLEPTICS                    | 21            | -                  | 1         | 2                          | 1         | -        | -        |
| CARDIOVASCULAR DRUGS            | 25            | 2                  | 4         | 3                          | 3         | -        | -        |
| ACETHAMINOPHEN                  | 10            | -                  | -         | -                          | -         | -        | -        |
| ANTICONVULSANTS                 | 50            | 1                  | 3         | 2                          | -         | -        | -        |
| NSAIDs and NONOPIOID ANALGESICS | 19            | -                  | -         | -                          | -         | -        | 1        |
| ANTIBIOTICS                     | 4             | -                  | -         | 1                          | -         | -        | -        |
| HYPOGLYCEMIC AGENTS             | 5             | -                  | -         | -                          | -         | -        | -        |
| OPIOIDS                         | 2             | -                  | -         | -                          | -         | -        | -        |
| TUBERCULOSTATICS                | 14            | -                  | -         | -                          | -         | -        | -        |
| OTHERS                          | 28            | -                  | -         | 1                          | -         | -        | -        |
| UNKNOWN DRUGS                   | 43            | 3                  | 2         | 1                          | 1         | -        | -        |
| <b>TOTAL</b>                    | <b>594</b>    | <b>9</b>           | <b>40</b> | <b>35</b>                  | <b>12</b> | <b>1</b> | <b>4</b> |

*EKG – electrocardiogram*

*SVD – supraventricular disturbances*

*VD – ventricular disturbances*

No life-threatening dysrhythmias and no deaths were reported due to cardiac toxic effects in our study.

The inter-rater score for categorical variables varied between 0.92 and 1, expressing a good inter-rater reliability.

## DISCUSSION AND CONCLUSIONS

This study provide informations about the frequency of arterial blood pressure changes and dysrhythmias in acutely drug poisoned patients admitted in the Toxicology Clinic of the Emergency Clinical Hospital Iasi, over a six years period. This study reflects the current state of matters encountered in a toxicology clinic. In certain cases, some of these disturbances could have been pre-existing and unknown to the patient, and the current poisoning could have aggravated previous dysrhythmias or blood pressure changes.

The most important finding of our research was that cardiac toxic effects are rare, hypertension being encountered in 6.6%, hypotension observed in 14.1% of patients, tachycardia documented in 26.5% of patients and bradycardia in 8.3%. Only 14.5 % of patients had rhythm and conduction disturbances, fact reported by other researchers too (5).

For both arterial blood pressure changes and rate disturbances, polimedication was the most frequently involved category. From intoxications involving single substances, following cardiovascular drugs, barbiturates were the most frequent in the etiology of hypotension.

Tachycardia was most frequently associated with ingestion of antidepressants, benzodiazepines

and anticonvulsants. Sinus tachycardia, the most common rhythm disturbance in antidepressants overdose, has a multifactorial etiology, including anticholinergic effects, increased norepinephrine release, and reflex tachycardia (in response to vasodilatation). Tachycardia is recognized to be a sign of significant toxicity in this acute poisoning (6).

Although antidepressant poisoning is known as a poisoning with important cardiac complications, this wasn't confirmed by our research, possibly due to the limited number of cases. Marketing of newer and safer categories of antidepressants, with less cardio-toxic effects, could also explain our findings.

Barbiturates, cardiovascular drugs and benzodiazepine poisoning were mostly involved in the etiology of bradycardia.

Barbiturates induce cardio-vascular depression secondary to a negative inotropic effect and sodium channel-blocking action, followed by hypotension and bradycardia. Our results support this toxicological mechanism. (7).

Cardiovascular drugs involved in acute poisonings in our study were calcium channel blockers, beta blockers, angiotensin converting enzyme inhibitors, diuretics, nitrates, digitalis, angiotensin II receptor antagonists, antiarrhythmics. Bradycardia in such intoxications has multiple explanations, such as directly interacting with myocardial membranes and receptors or an indirect cardio-depressant effect, altering autonomic output or causing reflex changes in the heart (8).

Cardiac toxic effects of benzodiazepines come as the result of reducing the sympathetic tone and increasing the parasympathetic tone. Previous stud-

ies have shown that both hypotension and bradycardia are clinical features in this type of poisoning (9). In our study, benzodiazepines poisonings are accompanied more often by tachycardia, facts cited in severe acute poisonings (10).

Tuberculostatics poisonings were accompanied by both hypotension and tachycardia in our study. The proposed mechanism for this might be a decreased catecholamine synthesis (11, 12).

In the case of poisoning by analgesics, arterial hypertension is cited as result of an increase in hydro-saline retention (13-16), fact encountered in our study, too.

All the cardiac toxic effects had a significantly increased incidence in the case of moderate clinical forms and coma when comparing to mild forms. The incidence of tachycardia and hypotension increased when alcohol was ingested concomitantly with the drugs involved. It is well known that alcohol co-ingestion aggravates the effects produced by

sedative-hypnotics, antidepressants and cardiovascular drugs. Ethanol itself is responsible for inducing tachycardia and cardiovascular collapse in moderate to severe clinical forms of acute poisoning (17).

In conclusion, cardiac toxic effects were not frequent in acute drug poisonings cases admitted in our clinic, associated especially to clinical forms of moderate severity and to cases of coma. No life-threatening situations and no death cases were found in our patients. Further studies concerning dysrhythmias, including larger numbers of patients are still necessary.

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