ORIGINAL ARTICLE

Poisonings by Cardiovascular Drugs in Yekaterinburg, Russia

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Abstract

Background: The pattern of poisoning in Russia may be different from other countries. The study objective was to describe the pattern of poisoning with cardiovascular drugs in a major industrial city in Russia, Yekaterinburg.
Methods: This study was part of a larger prospective multi-center study including all acute poisonings in patients older than 15 years of age in the city of Yekaterinburg, during March 2009 to March 2010. Patients with main diagnosis of acute poisoning by cardiovascular drugs and two other commonly used drugs affecting cardiac system were included.
Results: Cardiovascular drugs were the main poisoning agent in 269 cases of 3,112 acute poisonings (8.6%) during the study period. Median age of the patients was 36 (range: 16-88) years and 108 patients (40%) were men. Over 85% of patients required hospital admission and ICU care was needed for 45.7% of patients. Men significantly outnumbered women in veratrine poisoning ($P < 0.001$) while women significantly outnumbered men in clonidine ($P < 0.001$), drotaverine ($P < 0.001$), CCB ($P < 0.001$) and beta blocker ($P = 0.012$) poisoning. The most frequent complications were hypotension (83 patients; 30.8%), cardiac arrhythmias (22 patients; 8.2%) and QT prolongation (5 patients; 1.9%). The main agents significantly associated with hypotension were the phenylalkylamine and benzothiazepine subclasses of CCBs (verapamil/diltiazem), veratrine, beta blockers, nitrates, ACE inhibitors, clonidine, and adelphan. In total, mortality rate was 4.1%. The highest rate of death was recorded for poisoning with verapamil/diltiazem (20%) followed by dihydropyridine subclass of CCBs (9.1%).
Conclusion: The most common drugs causing hypotension and cardiac arrhythmias were clonidine, CCBs, drotaverine and the veterinary drug "veratrine". Drotaverine, clonidine and CCBs were the most common drugs causing death. Poisonings with these agents are rare in other countries. Measures to reduce the availability of drotaverine and veratrine should be taken in Russia.

Keywords: Calcium Channel Blockers; Cardiovascular Agents; Drotaverine; Poisoning; Russia

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INTRODUCTION

Epidemiological studies in toxicology usually report the pattern of poisonings divided into "pharmaceuticals", "illegal drugs", "alcohols", etc. Some studies divide "pharmaceuticals" to different classes such as "sedative-hypnotic", "cardiovascular", "anticonvulsant", etc. However, most epidemiological studies do not focus on the drugs included within a specific class. In many countries, calcium channel blockers (CCBs) and beta blockers are the most common cardiovascular drugs involved in acute poisonings. The severe complications in overdose with these drugs are well known and described in several publications (1-3). However, in Russia, the pattern of drugs causing cardiovascular complications in overdose is different due to the availability of some drugs and different traditions of self-treatment.

There are few publications presenting data on poisonings in Russia. They include an analysis of alcohol- related deaths (4), a large case series of exposures to high level of acetic acid (5), and an old epidemiologic study on poisonings in 2001 (6). The study in 2001 reported three main groups of toxic agents causing poisonings in Russia (6). They were pharmaceuticals (up to 63%), alcohols (up to 49%) and corrosives (up to 22%), but varied in different Russian cities (6). A ten-year study (2002-2011) on 26,783 poisoning cases from the Russian city "Perm" showed that pharmaceuticals were responsible for 52%, alcohols for 24% and acetic acid for 7% of the cases. In this study, cardiovascular drugs accounted for 7% of the pharmaceutical poisonings (7).

A few publications have described the risk of poisoning from so-called "Russian drugs" (8,9). Drugs like drotaverine and phenazepam are widely used and sold without prescription in Russia. Self-poisonings and suicide attempts with these drugs are frequent. Russian emigrants may also use these drugs in their new country of residence as these drugs

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are widely available on the internet, so it is important for physicians to be aware of their toxicity and how to manage these cases. In addition, criminal cases of clonidine poisoning, which are well known in Russia, occasionally happen in Europe (8). Despite these facts, there has been no comprehensive study on the pattern of poisoning with cardiovascular drugs in Russia. Thus, we aimed to evaluate the pattern of poisoning by cardiovascular drugs during one year in a major industrial city in Russia, Yekaterinburg.

METHODS

Study design and catchment area

The study was part of a larger one-year prospective multi-center study in the city of Yekaterinburg. Patients older than 15 years with a main diagnosis of acute poisoning managed either outside hospital or in the hospitals (both intentional and unintentional) were included prospectively from the beginning of March 2009 to the beginning of March 2010. Children and adolescents with 15 years of age and under are treated in pediatric hospitals and their data were unavailable to the investigators. Patients living in cities other than Yekaterinburg but referred to the Poison Treatment Centers (PTCs) in this city were excluded from the analysis. Chronic poisonings and patients with co-ingestions or another main diagnosis such as trauma were also excluded.

Physicians in ambulances or hospitals initially diagnosed and managed all poisoning cases. The toxic agent was confirmed by laboratory identification in the PTCs or at the Forensic Institute. Patients discharged from ambulances were the only cases not confirmed with laboratory testing. A predesigned checklist similar to those used in the Oslo intoxication studies in 2003 and 2008 were used (10,11). The checklists were completed by ambulance physicians, toxicologists in hospitals, and forensic specialists at the Forensic Institute. To ensure full inclusion, the patient lists were checked by coordinators at two PTCs and at the ambulance service in Yekaterinburg. The population of Yekaterinburg as of January 2010 was about 1,344,000, of whom 1,145,000 were aged 16 years and older.

The system of acute poisoning care in Yekaterinburg

Poisoned patients requiring hospitalization are transferred by ambulance to one of the two PTCs located in opposite outskirts of Yekaterinburg. Only 4-5% of patients might be admitted to other hospitals. The PTCs consist of an observation unit, an intensive care unit (ICU), toxicological laboratories and a poison information service. The ambulance service includes ordinary ambulances and specialized ambulances. Ordinary ambulance personnel included physicians specialized in general ambulance service. Three types of specialized ambulances are staffed by physicians specialized in resuscitation, psychiatry or cardiology. The majority of acutely poisoned patients were treated by ambulance personnel including physicians specialized in resuscitation, capable of providing artificial lung ventilation and central vein access.

Classification of cardiovascular drugs

The main toxic agent (poisoning agent) was defined as the substance thought to be most toxic in the amount taken, based on the research coordinators' qualified judgment. The main agent was determined based on information taken from the patients or relatives, clinical observations, and, if applicable, findings at the scene of the overdose. Toxicological testing was performed for hospitalized patients and for subjects found dead on scene. Gas chromatography with mass spectrometry (GC-MS) or thin layer chromatography was used for pharmaceutical agent identification.

Cardiovascular drugs were defined as medications prescribed for the treatment of arterial hypertension, cardiac dysrhythmias, cardiac ischemia and cardiac insufficiency. Additionally, the spasmolytic agent drotaverine and the veterinary drug veratrine were included in this study, because these agents often cause cardiovascular disturbances.

CCBs were divided into three groups based on differences in their pharmacological profile and clinical symptoms. The first group included phenylalkylamines and benzothiazepines, the second included dihydropyridines and the third diphenylpiperazines.

Consciousness status was classified according to the Glasgow Coma Scale (GCS): alert (GCS score: 15); confusion or drowsiness (GCS: 13-14); moderately impaired consciousness (GCS: 8-12); and severely impaired consciousness (GCS < 8) (12). Respiratory insufficiency was defined as a clinical need for ventilatory support. Hypotension was defined as a systolic blood pressure below 85 mmHg in at least two separate measurements. Cardiac arrhythmias were registered by electrocardiogram (ECG). Conduction disturbances were classified as arrhythmias, but sinus tachycardia was not. QTc prolongation was defined as > 430 msec in men and > 450 msec in women, and QRS widening was defined as > 100 msec. Cardiac arrest was classified independently and not as an arrhythmia. Poisoning intentions were defined as accidental, suicidal and criminal.

Ethics

Treatment was given according to standard guidelines. The study did not interfere with the process of admission and medical care required for the patients. No patient received additional interventions. The study was performed in accordance with the Helsinki Declaration and approved by the Institutional Ethics Committee of the Ural State Medical Academy. The anonymity of patients' information was maintained.

Statistical analysis

Statistical analyses were performed using SPSS software, version 16 (SPSS Inc., Chicago, Illinois). Multivariate logistic regression analysis was performed to define toxic agents associated with risk of hypotension. P values less than 0.05 were considered statistically significant.

RESULTS

General pattern

There were a total of 3,112 acute poisonings referred to the two PTCs during the study year, giving an incidence of 2.7 per 1,000 for the city's population aged 16 years or older. Cardiovascular drugs were the main toxic agent in 269 cases (8.6%), of which, 230 cases were hospitalized, 35 were discharged after ambulance treatment, and four were found dead on scene (all of whom were due to drotaverine poisoning). Median age of the patients was 36 (range: 16-88)

years and 108 patients (40%) were men. Table 1 shows the gender distribution of poisoned patents with different cardiovascular drugs in Yekaterinburg. Men significantly outnumbered women in veratrine poisoning (P < 0.001) while women significantly outnumbered men in clonidine (P < 0.001), drotaverine (P < 0.001), CCB (P < 0.001) and beta blocker (P = 0.012) poisoning.

Detailed report of some drugs

- *Clonidine*

There were 55 poisoning cases with clonidine as the main toxic agent. Median age was 58 (range: 16-88) years and 78.1% were women. Eighty percent were suicide attempts, 15% were accidental, and 5% were criminal. In 74.5% of the cases, clonidine was confirmed by laboratory tests. Additional agents were found in 24 cases (43.6%); including alcohol in 12 and other medications in 12 cases. Median duration of hospital stay was 3 (range: 0-22) days.

On admission, 14 of 51 hospitalized patients had hypotension and 15 patients had cardiac arrhythmias. QT prolongation was present in nine, and QRS widening was noted in three cases. Twenty-two patients presented with reduced consciousness; five were confused or drowsy, eleven were in a moderately impaired consciousness and six were in severely impaired consciousness. Of those six patients with severe impaired consciousness, ethanol was found in one case (blood alcohol level: 0.27 g/L), benzodiazepines in one case, and phenobarbital in another. These six patients developed respiratory failure requiring mechanical ventilation for up to ten days. Three of the six patients died, of which all were women aged 72, 80 and 88 years.

- *Calcium channels blockers*

CCBs were the poisoning agents in 24 cases including dihydroperidines in 11 cases, phenylethylamines (verapamil) and benzothiazepines (diltiazem) in 10 cases, and diphenylpiperazines in 3 cases. Median duration of hospital stay was 3 (range: 1-7) days. All the 10 poisoning cases by phenylethylamines and benzothiazepines were seen in women with median age of 23 (17-80) years. The poisonings by phenylethylamines and benzothiazepines were considered suicide attempt in 8 cases and accidental in 2 cases. Six cases were laboratory verified. In one case, phenazepam and clonidine were also found. Hypotension developed in 8 of 10 non-dihydroperidines poisoned cases and complete isorhythmic atrioventricular dissociation in 3 cases. On admission, 5 of 10 hospitalized patients were alert, 4 patients were in moderately and 1 was in severely impaired consciousness. No sedatives or other pharmaceutical co-ingestions were found in these cases, only a blood alcohol level of 0.4 and 0.93 g/L in 2 cases. One patient had taken 90 tablets of diltiazem and was admitted in a circulatory shock and coma, who later developed acute renal failure (ARF) and lung edema. She did not respond to vasopressors but was successfully treated with insulin/glucose and lipid emulsion therapy (LET). She developed pneumonia, and required prolonged mechanical ventilation and hemodialysis, but had a full recovery without residual renal failure or brain damage, and was discharged 32 days post-admission. Two female patients aged 56 and 72 years died on the 6th and 7th day post-admission. Both had hypotension, QT prolongation and hypoxic brain damage on admission.

There were 11 poisonings with the dihydroperidines, nifedipine and amlodipine. Median age of these patients was 42 (range: 21-66) and 10 of them were women. Ten cases were suicide attempts, while one was accidental. In 7 cases, the toxic agent was confirmed by laboratory tests. An additional agent was found in 6 cases including barbiturates, drotaverine, benzodiazepines and alcohol. One case was

Table 1. Gender distribution of patients and lab confirmation plotted against cardiovascular drugs

Main poisoning agent	Total; n (%)	Gender		P value	Verified cases with lab test; n (%)
		Male (n = 108), n (%)	Female (n = 161), n (%)		
Veratrine	56 (20.8)	51 (47.2)	5 (3.1)	< 0.001	34 (60.7)
Clonidine	55 (20.4)	12 (11.1)	43 (26.7)	< 0.001	41 (74.5)
Drotaverine	51 (19.0)	13 (12.0)	38 (23.6)	< 0.001	37 (72.5)
ACE* inhibitors	24 (8.9)	10 (9.3)	14 (8.7)	0.414	16 (66.7)
Calcium channel blockers	24 (8.9)	2 (1.9)	22 (13.7)	< 0.001	15 (62.5)
Adelphan	18 (6.7)	6 (5.6)	12 (7.5)	0.157	12 (66.7)
Beta blockers	16 (5.9)	3 (2.8)	13 (8.1)	0.012	6 (37.5)
Nitrates	14 (5.2)	3 (2.8)	11 (6.9)	0.330	7 (50.0)
Diuretics**	2 (0.7)	1 (0.9)	1 (0.6)	~ 1	2 (100)
Methyldopa	1 (0.4)	0 (0)	1 (0.6)	~ 1	0 (0.0)
Cardiac glycosides	1 (0.4)	1 (0.9)	0 (0.0)	~ 1	0 (0.0)
Unknown or other	7 (20.6)	6 (5.6)	1 (0.6)	0.059	1 (14.3)
Total	269 (100)	108 (100)	161 (100)	---	171 (63.6)

* Angiotensin converting enzyme
** Indapamid, spironolactone

complicated with marked hypotension (60/40 mm Hg), QRS widening (120 msec) and QT prolongation (500 msec) on admission, and respiratory failure within 15 hours of admission. This 66-year-old woman with amlodipine and phenazepam poisoning was ventilated and underwent insulin/glucose therapy, but died during the first day. The other patients did not show severe symptoms.

- *Angiotensin converting enzyme inhibitors*

There were 24 poisonings by ACE inhibitors including enalapril in 21 and lisinopril in 3 cases. Median age of patients was 33 (range: 20-60) years and 14 cases were women. Eighteen cases were due to suicide attempts and the remaining cases were accidental. Laboratory verification was obtained in 16 cases. Three patients were confused or drowsy. Eight patients were hypotensive. Five patients were discharged from the ambulance without further transport. No cases of ARF caused by ACE inhibitors were found. Median duration of hospital stay was 2 (range: 0-5) days.

- *Beta blockers*

There were 16 poisonings with beta blockers as the main toxic agent including propranolol in 5 cases, atenolol in 5, metoprolol in 4, bisoprolol in one and unspecified beta-blocker in one case. Median age was 41 (range: 24-83) years and 13 were women. Laboratory confirmation was obtained in 6 cases. Additionally, GC-MS showed salicylates in 2 cases, nonsteroidal anti-inflammatory drugs (NSAIDs) in 2 cases, vinpocetin in one case, and ethanol in one case. The main symptoms were hypotension occurring in 7 cases, and both hypotension and first degree heart block in one case. Bradycardia was found in one case. Of the 14 patients brought to hospital, three were confused or drowsy on admission. All patients survived. Two patients were discharged from ambulance by the ambulance physicians without further transport. Median duration of hospital stay was 3 (range: 1-8) days.

- *Adelpane*

Adelpane (consisting of 0.1 mg reserpine, 10 mg dihydralazine and 10 mg hydrochlorothiazide) was the main poisoning agent in 18 cases, 17 of which were hospitalized. Median age was 38 (range: 19-78) years and 12 were women. Twelve cases were laboratory confirmed. Moreover, ethanol was also found in 3 cases and acetaminophen in one case. Four patients had hypotension while one had hypothermia. Two patients were drowsy on admission; one of them had a blood alcohol level of 0.4 g/L. Median duration of hospital stay was 3 (range: 1-7) days.

- *Nitrates*

Nitrates were the main poisoning agent in 14 cases. Median age was 25 (range: 16-83) years and 11 were women. Seven cases were confirmed by laboratory investigations. An additional agent was found in 5 cases including ethanol in 2, salicylates in 2 and acetic acid in one case. Six patients were hypotensive. One 83-year old woman with isosorbide dinitrate poisoning was hypotensive and comatose on admission. She died on 12th day post-admission from lung complications. Postmortem examination revealed underlying lung cancer. Median duration of hospital stay was 2 (range: 1-7) days.

- *Drotaverine*

In 51 cases, drotaverine was responsible for poisoning. Median age of the patients was 24 (range: 16-70) years. An additional agent was found in 24 cases, most commonly salicylates or NSAIDs. Forty-eight cases were due to suicidal attempt and 3 were accidental. Four patients were found dead on scene, of which 2 were men, aged 41 and 22 years and 2 were women, aged 42 and 54 years. All deaths were due to suicide. Median duration of hospital stay was 1.5 (range: 1-3) days.

- *Veratrine*

There were 56 cases of veratrine poisoning. Median age of the patients was 43 (range 21-62) years and 51 cases were men. All poisonings were accidental. Forty-one patients were hospitalized, while 15 were discharged from the ambulance. Veratrine alkaloids were found in 34 urine samples. Ethanol was additionally found in 15 samples.

All patients vomited on admission. Other clinical features registered in ambulance or on hospital admission were hypotension in 32 patients, arrhythmia in 7 patients, QT prolongation in 4 patients and QRS widening in one patient. All patients developed bradycardia. Two patients were drowsy and two were in moderately impaired consciousness. Reduced consciousness was caused by ethanol co-ingestion, or severe hypotension in one case. In this case, a 62-year-old woman developed hypotension and first degree atrioventricular block. She was agitated on admission and developed partial muscle jerking in her legs and a combined metabolic and respiratory acidosis. One patient developed ARF due to prolonged hypotension before admission and rhabdomyolysis. He was treated with conventional hemodialysis for 26 days. Median duration of hospital stay was 2 (range: 1-48) days.

Treatments

Of 269 patients with cardiac drugs exposure, 253 patients (94.1%) required either out-of-hospital or in-hospital supportive and specific treatments (Table 2). Sixteen patients did not require treatment other than close observation. Intravenous fluids (81.4%) and gastric lavage (75.8%) were the most common treatments given to the patients. Only 17 patients (6.3%) required vasopressors. Nearly half of patients (45.7%) were admitted to ICU and 9 patients (3.3%) required mechanical ventilation.

Analysis of outcome

- **Hypotension:** Hypotension occurred in 83 patients (30.8%). But in 15 patients, the hypotension was transient and responsive to therapeutic measures given at the ambulance service. Analysis on the patients with marked hypotension who required hospital admission is shown in table 3. The main agents significantly associated with hypotension were the phenylalkylamine and benzothiazepine subclasses of CCBs (verapamil/diltiazem) (OR 90.5, 95% CI 18.4-445.6), veratrine (OR 24.6, CI 12.7-47.8), beta blockers (OR 19.4, CI 7.3-57.6), nitrates (OR 19.4, CI 7.3-57.6), ACE inhibitors (OR 18.8, CI 7.3-48.4), clonidine (OR 9.7, CI 5.0-19.0), and adelphan (OR 7.9, CI 2.5-25.1).

- **Rhythm abnormalities:** In total, 22 cases (8.2% of total cases) had cardiac arrhythmia (15 clonidine cases (15/55: 27.3%) and 7 veratrine cases (7/56: 12.5%)). In addition, 16 cases (5.9% of total cases) developed QT prolongation (9 clonidine cases (9/55: 16.4%), 4 veratrine cases (4/56: 7.1%),

Table 2. Treatments given to the patients according to the cardiovascular drugs taken

Main poisoning agent		Treatments									
	Total n. of patients	IV fluids; n (%)	GL; n (%)	Atropine; n (%)	AC; n (%)	Vasopressor; n (%)	MV; n (%)	Ca salt; n (%)	Insulin/ glucose; n (%)	LE; n (%)	CP; n (%)
Beta blockers	16	11 (68.8)	14 (87.5)	-	1 (6.3)	2 (12.5)	-	-	-	-	-
CCB; (verapamil/diltiazem)	10	8 (80.0)	6 (60.0)	3 (30.0)	3 (30.0)	5 (50.0)	2 (20.0)	6 (60.0)	3 (30.0)	1 (10.0)	
Clonidine	55	49 (89.1)	42 (76.4)	29 (52.7)	11 (20.0)	2 (3.6)	6 (10.9)	-	-	-	1 (1.8)
Drotaverine	51	42 (82.4)	42 (82.4)	2 (3.9)	4 (7.8)	1 (2.0)	-	-	-	-	-
Veratrine	56	47 (83.9)	29 (51.8)	32 (57.1)	1 (1.8)	4 (7.1)	-	-	-	-	-
Others	81	62 (76.5)	71 (87.7)	1 (1.2)	5 (6.2)	3 (3.7)	1 (1.2)	2 (2.5)	1 (1.2)	-	-
Total	269	219 (81.4)	204 (75.8)	67 (24.9)	25 (9.3)	17 (6.3)	9 (3.3)	8 (3.0)	4 (1.5)	1 (0.4)	1 (0.4)

GL: Gastric lavage, AC: Activated charcoal, MV: Mechanical ventilation, Ca: Calcium chloride/calcium gluconate, LE: Lipid emulsions, CP: Cardiac pacing

Table 3. Factors associated with hypotension (results of multivariate logistic regression analysis on hospitalized patients)

Main agent	Total n. of patients*	Hypotension; n (%)	OR	95% CI
Other toxic agents	1638	61 (3.7)	Ref	Ref
CCB; verapamil/diltiazem	9	7 (77.8)	90.5**	18.4 - 444.6
Veratrine	41	20 (48.8)	24.6**	12.7 - 47.8
Nitrates	14	6 (42.8)	19.4**	6.5 - 57.6
Beta-blockers	14	6 (42.8)	19.4**	6.5 - 57.6
ACE inhibitors	19	8 (42.1)	18.8**	7.3 - 48.4
Clonidine	51	14 (27.5)	9.7**	5.0 - 19.0
Adelphan	17	4 (23.5)	7.9**	2.5 - 25.1
CCB; dihydropyridine	11	1 (9.1)	2.6	0.3 - 20.5
Drotaverine	46	2 (4.3)	1.2	0.3 - 4.7
Cardiac glycozides	1	0 (0.0)	-	-
CCB; diphenylpiperazines	2	0 (0.0)	-	-
Diuretics (indapamid, spironolactone)	2	0 (0.0)	-	-
Methyldopa	1	0 (0.0)	-	-
Unknown agents	2	0 (0.0)	-	-

* Only hospitalized patients were included in this analysis.
** $P < 0.001$

2 verapamil/diltiazem cases (2/10: 20%) and one dihydroperidine CCB case (1/11: 9.1%)), and 5 cases (1.9% of total cases) developed QRS widening (3 clonidine cases (3/55: 5.5%), 1 veratrine case (1/56: 1.8%), and 1 dihydroperidine CCB case (1/11: 9.1%))**.**

- Hospitalization and ICU admission: Over 85% of patients required hospital admission and ICU care was needed for 45.7% of patients. Except methyl dopa and cardiac glycoside that were the main poisoning agent for one patient each and for both cases no death was recorded, the highest rate of hospitalization was found for poisoning with dihydropyridine subclass of CCBs (100%) and nitrates (100%) (Table 4). The highest rate of ICU admission was seen in poisoning with dihydropyridine subclass of CCBs (72.7%) and clonidine (65.5%).

- Death: In total, approximately 4% of cases resulted in death. The highest rate of death was recorded for poisoning with verapamil/diltiazem (20%) followed by dihydropyridine

Table 4. Outcome of patients

Main poisoning agent	Total n. of patients	Hospitalized patients; n (%)	ICU admission; n (%)	Death; n (%)
ACE inhibitors	24	19 (79.2)	9 (37.5)	0 (0.0)
Adelphan	18	17 (94.4)	9 (50.0)	0 (0.0)
Beta blockers	16	14 (87.5)	9 (56.3)	0 (0.0)
Cardiac glycozides	1	1 (100)	1 (100)	0 (0.0)
CCB; diphenylpiperazines	3	2 (66.7)	0 (0.0)	0 (0.0)
CCB; verapamil/diltiazem	10	9 (90.0)	6 (60.0)	2 (20.0)
CCB; dihydropyridine	11	11 (100)	8 (72.7)	1 (9.1)
Clonidine	55	51 (92.7)	36 (65.5)	3 (5.5)
Diuretics*	2	2 (100)	0 (0.0)	0 (0.0)
Drotaverine	51	46 (90.2)	13 (25.5)	4 (7.8)
Methyldopa	1	1 (100)	1 (100)	0 (0.0)
Nitrates	14	14 (100)	6 (42.9)	1 (7.1)
Veratrine	56	41 (73.2)	24 (42.9)	0 (0.0)
Unknown hypotensive agents	7	2 (28.6)	1 (14.3)	0 (0.0)
Total	269	230 (85.5)	123 (45.7)	11 (4.1)

* Indapamid, spironolactone

subclass of CCBs (9.1%).

DISCUSSION

Cardiovascular drugs, drotaverine and veratrine were involved in 8.6% of all adult poisonings in Yekaterinburg during 2009 to 2010 as shown in our study. In comparison, cardiovascular drugs were the cause of just 1% of poisonings in a study from Mashhad, Iran (13), and 6% in a study from the USA (14). In a study from Oslo (Norway), cardiovascular drugs were involved in 3% of all adult poisonings (15). The poisoning patterns in these countries differed from what found in our study. In this respect, CCBs and beta blockers accounted for 40% of poisonings by cardiovascular drugs and 50% of deaths from cardiovascular medications in the USA in 2008 (16). However, in our study these medications caused only 14.9% of the cardiac drugs poisonings but similarly 42.9% of the deaths.

In the present study, clonidine and drotaverine contributed to 20.4% and 19% of the cases, respectively. The in-hospital mortality of clonidine poisonings was 5.5% in our study and accounted for 42.9% of all deaths by cardiovascular drugs. Nearly six percent of clonidine poisonings in the present study were following criminal attempts, where clonidine was used by Russian streetwalkers in order to rob a client. This situation rarely appears in Europe (8). Moreover, we found adelphan, an old antihypertensive agent, surprisingly often as the main toxic agent. Drotaverine (No-Spa®) is a well-known antispasmodic agent in Russia and is sold without prescription. This drug is not used for cardiovascular diseases, but its spasmolytic effect is due to Ca^{++} depletion similar to diltiazem (17). It is typically used against gastrointestinal colic, renal colic, and menstrual cramps. It is a frequent cause of poisoning in Russia, because people consider it non-toxic. Case reports of drotaverine-associated deaths have been described in this country several years ago (18,19), where the authors found signs of sudden death in the postmortem examination. Drotaverine caused the majority of deaths by cardiovascular drugs in our study and all deaths by this drug were found at home (20). Those brought to hospital only had mild poisoning or were asymptomatic. This is consistent with the pattern described in recent publications (21,22). Informing the public of the dangers of drotaverine, e.g. by changing the packet labelling, may be a way of reducing these deaths. Similar to drotaverine, veratrine poisonings only sporadically happen in Europe (23), while 15.2% of poisoning in the present study was due to this drug. Veratrine is the active ingredient in the plant Hellebore (Chemeritsa in Russian language), being used in Russia as an emetic in veterinary medicine.

In this study, gastric lavage was performed for 75.8% of the cases, as compared to 9% in a Norwegian and 2% in a Dutch study (10,24). This considerable difference in practice may be explained by a tradition in Russia to gastric lavage all poisoned patients. As a general rule, gastric lavage was performed by the ambulance service at home (25). However, only a small proportion of the patients were lavaged within 1 hour after intake, which is generally considered the beneficial time limit. Although no complications were recorded in this study, the practice of routine gastric lavage cannot be advocated due to risk of complications, mainly aspiration (26). LET also known as lipid rescue therapy and high-dose insulin therapy were effective to save life of a patient with massive diltiazem overdose in the present study. Bekjarovsky similarly reported successful treatment of a patient who had ingested 100 pills of sustained-release verapamil with LET and high-dose insulin (3). Nonetheless, use of high dose

insulin alone for CCB overdose might be ineffective in some cases, as we had a patient with amlodipine overdose who failed to survive even though she received this treatment. This fact has been supported by systematic reviews (27), despite promising outcomes after insulin therapy for majority of CCB poisonings.

LIMITATIONS

The present study included both pre-hospital and hospital data. Because of the short observation time and lack of follow-up on patients who were not transported to a hospital, the evaluation of complications from the pre-hospital phase was limited. Only Forensic Institute data of one-month mortality of those discharged from ambulances were checked. No one died during this one-month period. The data presented in the paper are 6 years old. However, no change in the pattern of poisoning with cardiac drugs has occurred according to our observations. In this sense, the results are still useful for policy making and health planning. Routine laboratory verification was only performed in those hospitalized or found dead on scene. Moreover, laboratory confirmation was difficult for some water-soluble agents because only GC-MS and thin-layer chromatography were available. While additional agents were registered in the hospital part of this study, only main agents were registered for the patients treated by the ambulance service.

CONCLUSION

The most common drugs causing hypotension and cardiac arrhythmias were clonidine, CCBs, drotaverine and veratrine. Drotaverine, clonidine and CCBs were the most common drugs causing death. Poisonings with these agents are rare in other countries. Measures to reduce the free availability of drotaverine and veratrine should be taken in Russia.

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